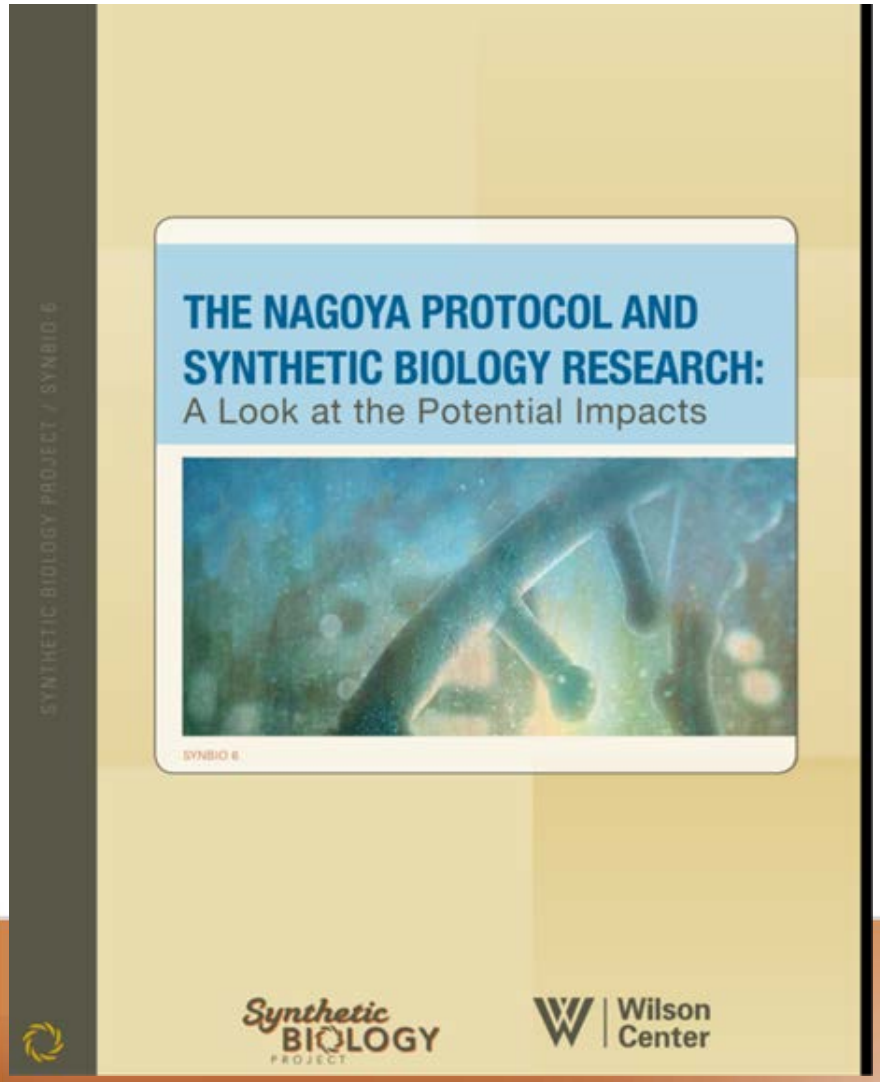
DIGITAL DNA: THE NAGOYA PROTOCOL, INTELLECTUAL PROPERTY TREATIES, AND SYNTHETIC BIOLOGY

Margo A. Bagley
Hardy Cross Dillard Professor of Law
Joseph C. Carter, Jr. Research Professor of Law
University of Virginia School of Law
mbagley@virginia.edu

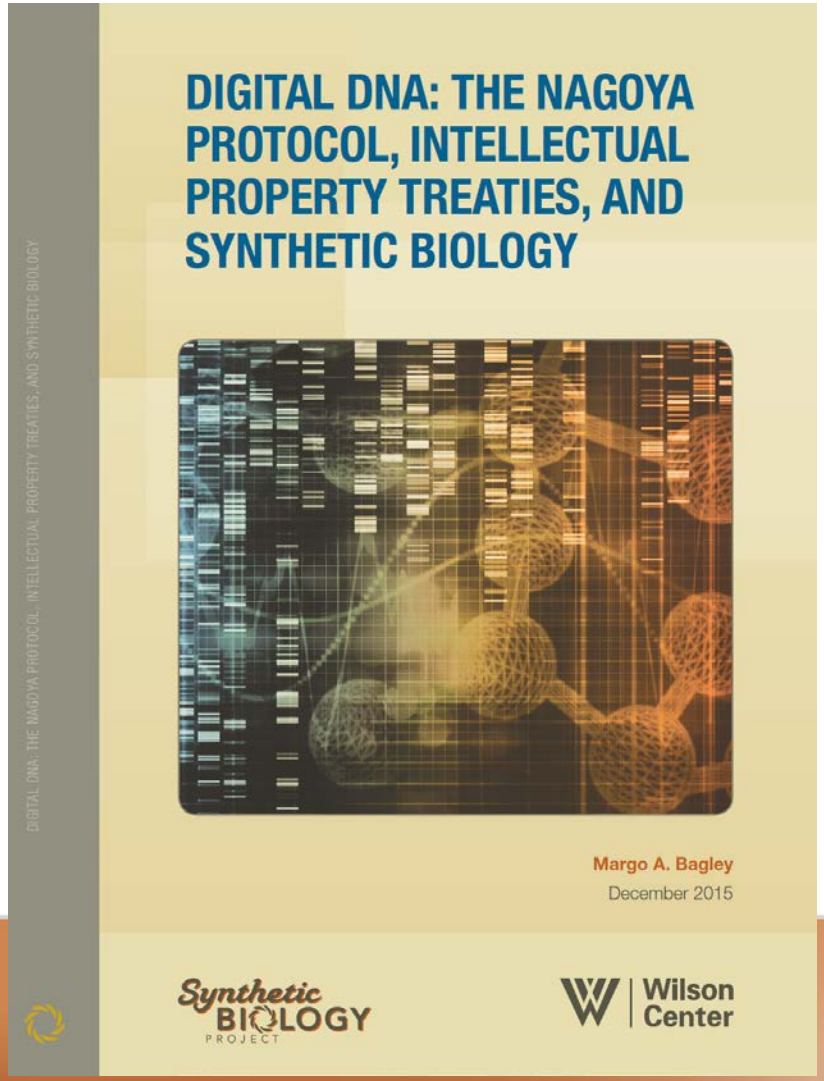
2013 WILSON CENTER REPORT (WITH ARTI RAI) ON THE NAGOYA PROTOCOL AND SYNTHETIC BIOLOGY: A LOOK AT THE POTENTIAL IMPACTS



- Synthetic Biology and Genetic Resources
- The Convention on Biological Diversity (CBD) and the Nagoya Protocol (NP)
- NP Implementation Issues
  - Pre-NP legislation
  - Temporal Scope
  - Breadth of Coverage

UNIVERSITY of VIRGINIA SCHOOL OF LAW

2015 WILSON CENTER REPORT ON DIGITAL DNA: THE NAGOYA PROTOCOL, INTELLECTUAL PROERTY TREATIES, AND SYNTHETIC BIOLOGY



- Overview of Synthetic Biology
- Synthetic Biology and Intellectual Property Protection
- Synthetic Biology and the Nagoya Protocol
  - Use and Misuse of Digital Information
  - Synthetic Biology, The Nagoya Protocol, and Intellectual Property Treaties
  - Possible Future Treaty based ABS/DOO Obligations

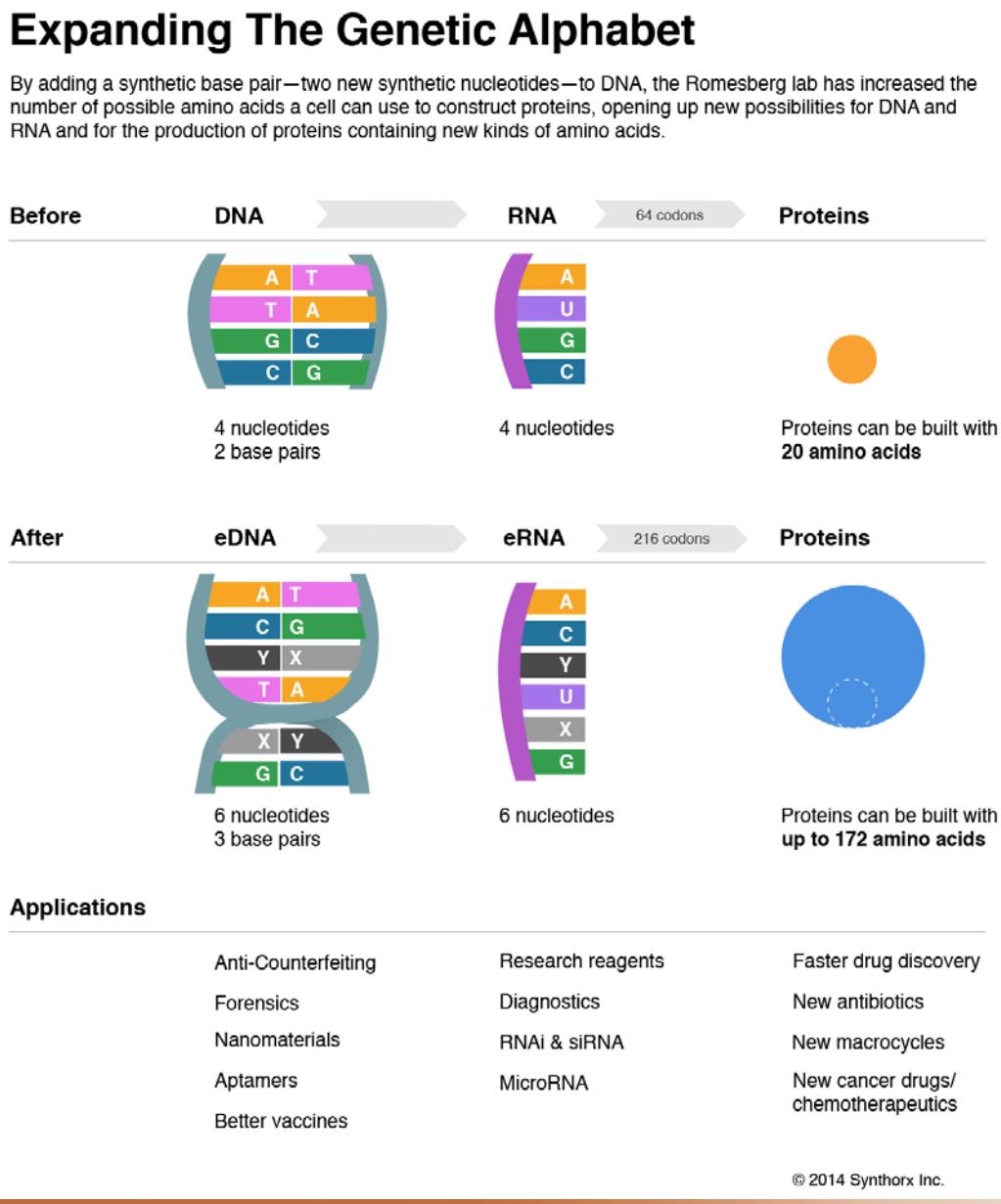
UNIVERSITY of VIRGINIA SCHOOL OF LAW

WHAT IS SYN BIO? NO SINGLE DEFINITION

- The creation of standardized biological parts that can be assembled into more complex modules to perform particular functions

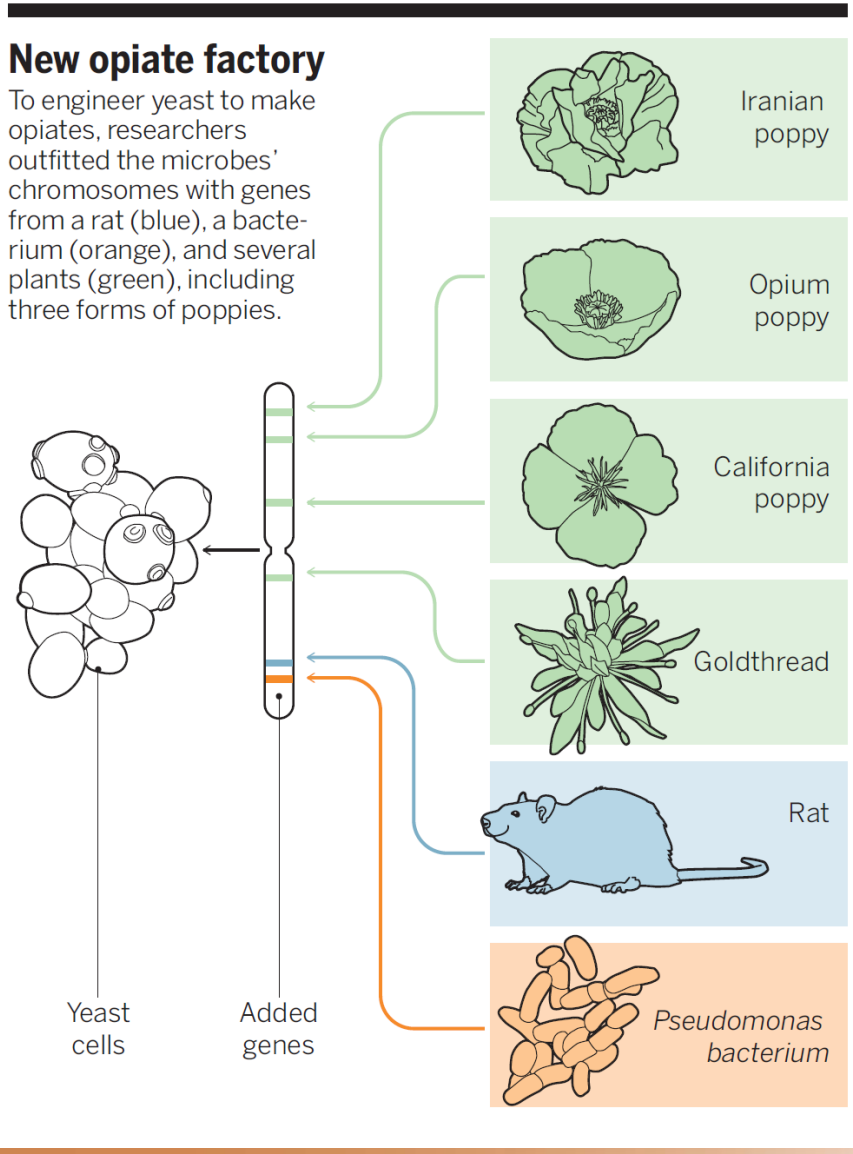
- "Top down" and "bottom up" approaches
- Synthetic biologists may eventually be able to construct entirely new biological systems; initial commercial applications, however, focus on replicating and modifying naturally occurring molecules.

“REVOLUTIONARY” SYNTHETIC BIOLOGY



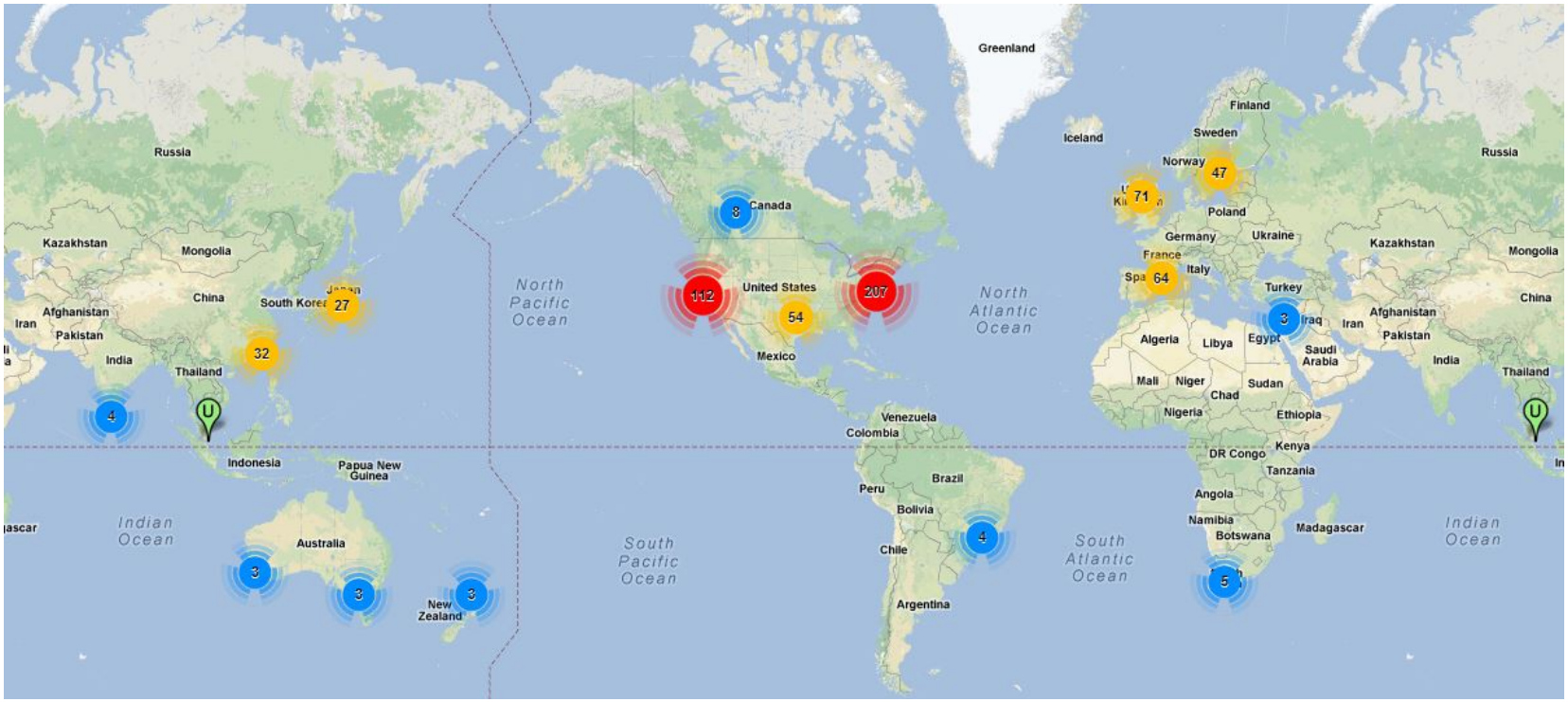
- “New” chromosome with synthetic nucleotides (new base pair)
- Could lead to creation of new proteins, cures

PRODUCING OPIATES WITH YEAST



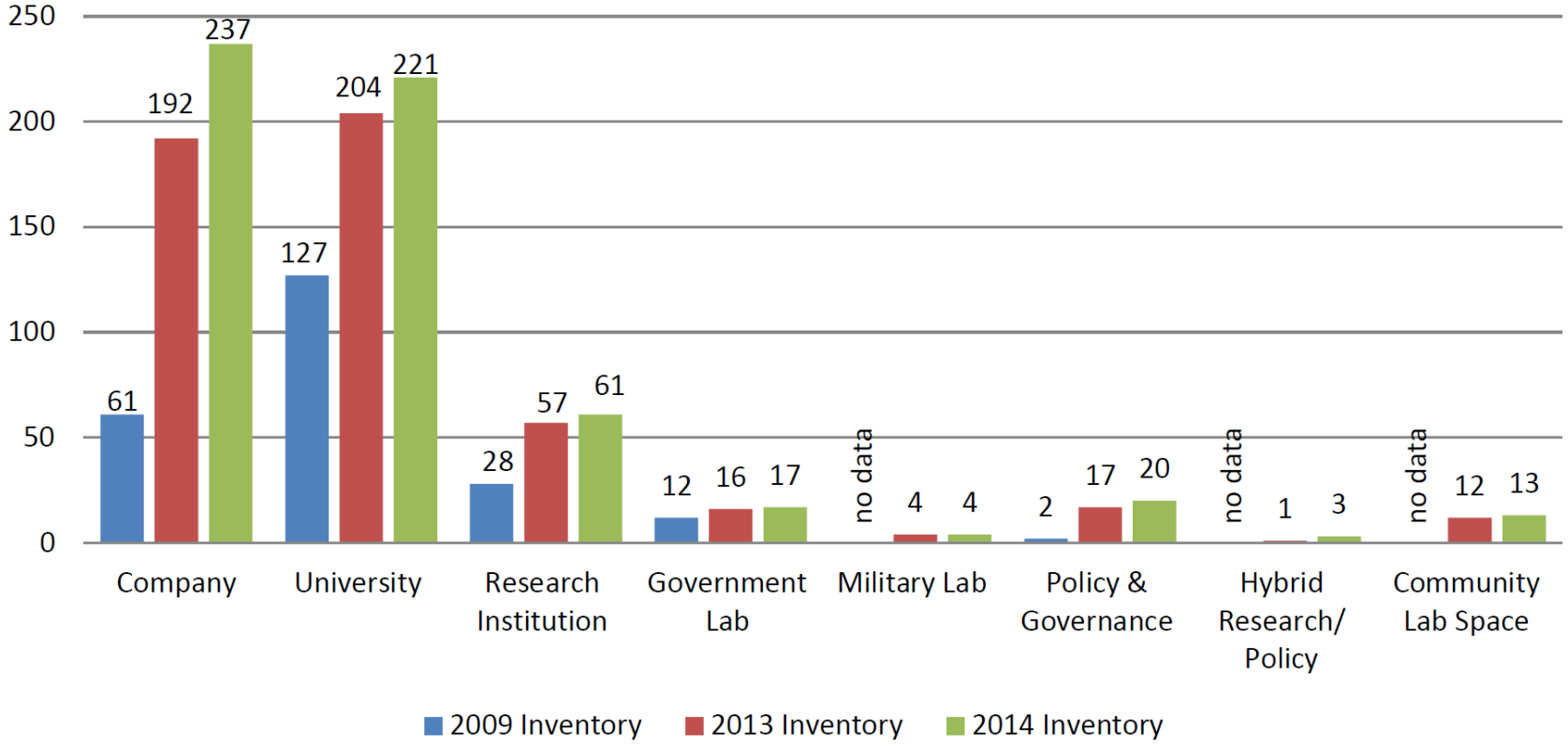
R. Service, Modified Yeast Produces Opiates from Sugar, Science Aug. 2015

WILSON CENTER "SYN BIO MAP" 2013



UNIVERSITY of VIRGINIA SCHOOL OF LAW

Fig 1. Entities Conducting Research in Synthetic Biology Worldwide



U.S GOVERNMENT SB FUNDING (2008-2014)

Private Sector:
$500M in 2015 alone

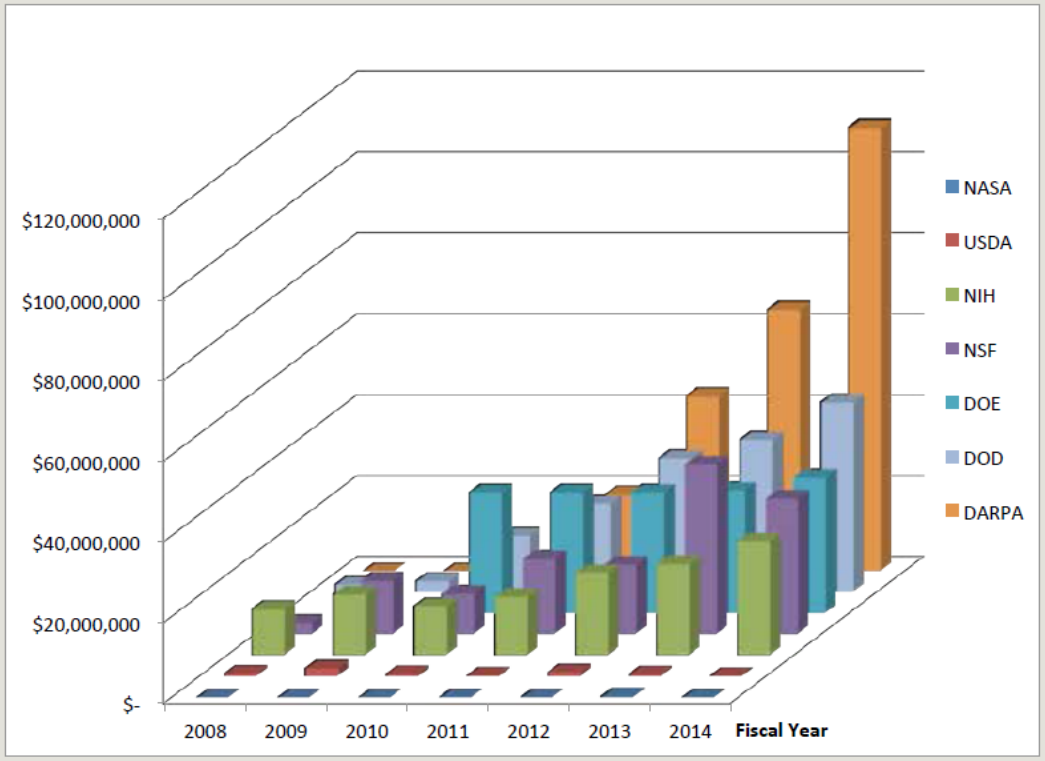


Fig. 1. Total U.S. Agency Funding by Fiscal Year

Registries of "standard" biological parts

(courtesy of Linda Kahl)

jbei
Joint BioEnergy Institute

SEVA Standard EuropeanVector Architecture

SynBERC
Synthetic Biology Engineering Research Center

biofab

PlantFab
Cambridge

ATCC
The Global Bioresource Center™

BCCM™

DSMZ
Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH

EUROSCARF

DNASU
PLASMID REPOSITORY

addgene
A better way to share plasmids

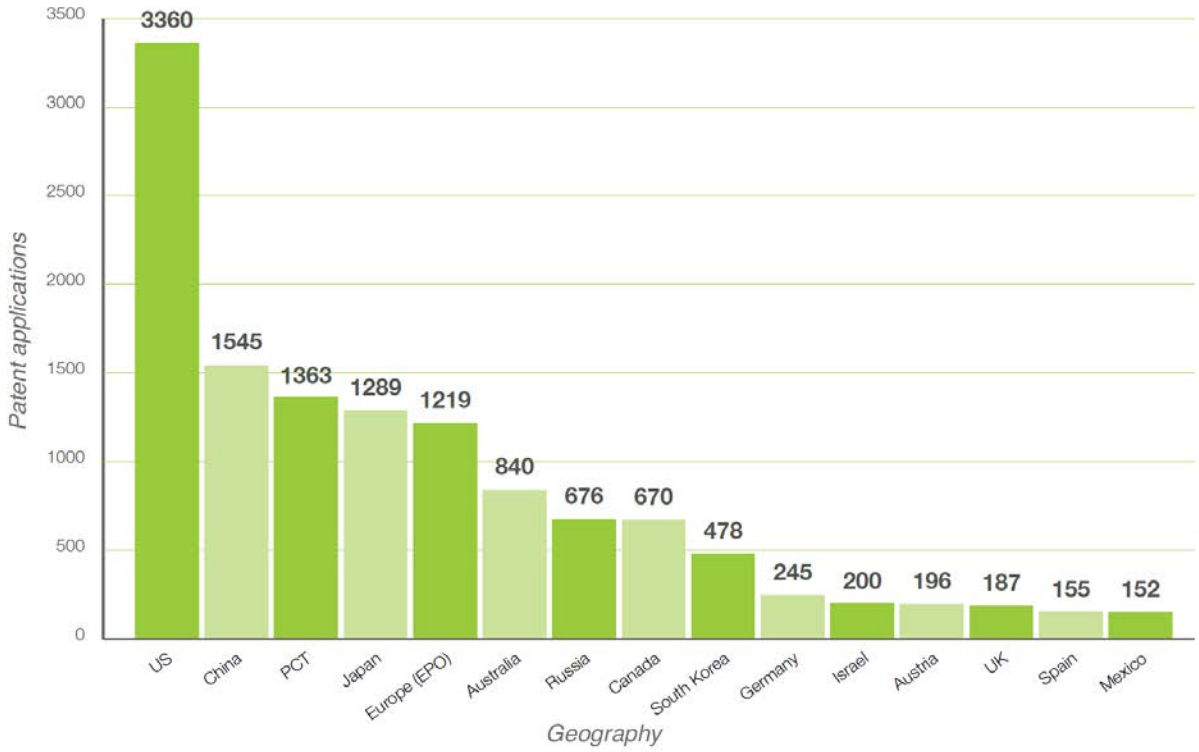
AMYRIS

UNIVERSITY of VIRGINIA
SCHOOL OF LAW

Synthetic Biology and Intellectual Property Protection

PATENTS LIKELY TO CONTINUE AS KEY FORM OF PROTECTION

Fig. 16: Total patent applications since 2003 by geography for synthetic biology inventions

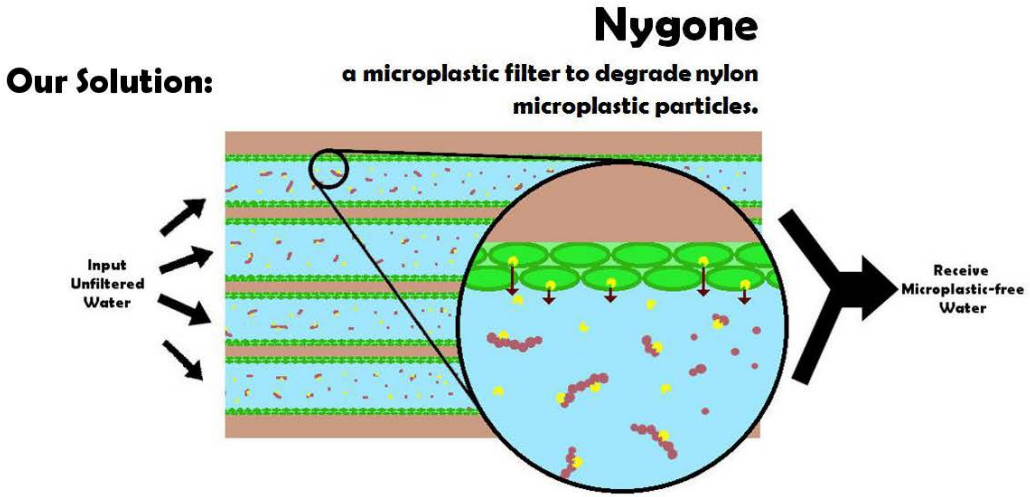


SYN BIO AND IP, KEY AREAS OF CONTROVERSY: PATENTS AND COPYRIGHTS

- Patents: Some SB inventions that copy existing compounds may not be patent-eligible in U.S. or Australia (*Myriad Genetics* cases);
- Copyright: Some advocate for copyright protection for SB DNA sequences to allow open source licensing
  - U.S. Copyright Office rejected so far

UVA IGEM TEAM: NYGONE

- 32 billion tons of plastic discarded in U.S. in 2012, 3 billion reclaimed
- **Team engineered a non-pathogenic bacteria to form a biofilm for wastewater filters using parts from registry**
- "we believe that other plastic degrading plasmids from the iGEM registry could be implemented in the same filter. This addition would allow for the optimization of a filter that could degrade all microplastics in the water supply."



http://2014.igem.org/Team:Virginia/Parts

UNIVERSITY of VIRGINIA SCHOOL OF LAW

Synthetic Biology and the Nagoya Protocol

ETHNOBIOLOGICAL RESEARCH AND "BIOPIRACY"

"[t]he patenting of plants, genes, and other biological products that are indigenous to a foreign country without compensating the keepers of those resources and the holders of knowledge appropriated during ethnobiological research processes."

H. Schmidt, mobot.org

ACCESS AND BENEFIT SHARING: THE CONVENTION ON BIOLOGICAL DIVERSITY (CBD)

- Unauthorized utilization and patenting of genetic resources/traditional knowledge – based inventions ("biopiracy") contributed to creation of the Convention on Biological Diversity (CBD). CBD has 196 Parties, in effect since 1993. Key Principles:
  - **States have sovereign control over biological resources within their borders** and shall ensure conservation of same
  - But states shall endeavor to create conditions to facilitate **access** on mutually agreed terms and subject to **prior informed consent, AND** there should be **fair and equitable sharing of benefits** of use of genetic resources with providing party (PIC/ABS)

- CBD provides for PIC/ABS but does not specify methodology
- Parties implemented widely varying legislation (or none at all) to comply
- Need for **uniform** framework, **enforceable** obligations on users, **reasonable** access provisions by providers

NAGOYA PROTOCOL TO THE CBD: ACCESS AND USER COMPLIANCE

- Adopted October 2010, **came into effect October 2014**
- **Framework** for **access** to genetic resources and traditional knowledge with **prior informed consent and on mutually agreed terms,** including terms on fair and equitable benefit sharing from ***utilization*** of genetic resources and associated traditional knowledge
- Among other things the Nagoya Protocol**:**
  - obligates Parties to **designate compliance checkpoints (Art. 17)**; and
  - "provide that genetic resources utilized within [their] jurisdiction" have been **accessed in accordance with** the domestic ABS/PIC/MAT requirements of another Party, and to **cooperate** in cases where another Party's domestic ABS legislation has been **violated** (Art. 15).

NP IMPLEMENTATION ISSUES FOR SYNTHETIC BIOLOGY RESEARCHERS

- "The Protocol significantly advances the Convention's third objective by providing a strong basis for **greater legal certainty** . . . For both providers and users of genetic resources" *NP Introduction*

BUT

- NP called "**a masterpiece in creative ambiguity**"* on topics where no consensus

- Implementation Issues:
  - Temporal scope
  - Breadth of coverage
  - EU issues
  - Compliance, etc.
- Considerable flexibility remaining in national law

*Oliva,(2011), cited in Ansari and Laxman, (2013)

Use and Misuse of Digital Information

NO NEED FOR TANGIBLE GENETIC STARTING MATERIAL

- [Registry of Standard Biological Parts]: "Although the registry **currently contains physical DNA**, its developers believe that, as DNA synthesis technology becomes increasingly inexpensive, the registry will be composed largely of **information and specifications that can be executed in synthesizers** just as semiconductor chip designs are executed by fabrication firms." Rai and Boyle (2007)

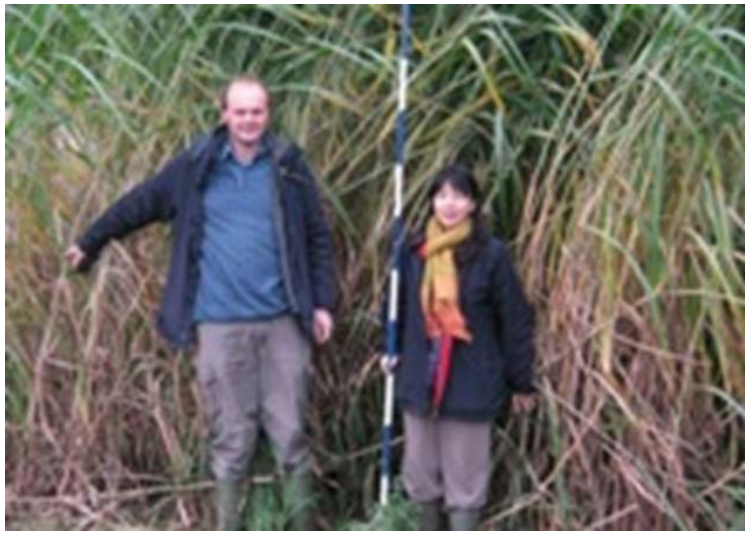
Symbol	BioBrick parts
	Promoter
	Coding sequence
	RBS
	DNA
	Inverter
	Plasmid backbone
	Terminator

NAGOYA PROTOCOL ART. 8: NON-COMMERCIAL USE

- Smithsonian Institution facilitated inclusion:
- "In the development and implementation of its access and benefit-sharing legislation or regulatory requirements, each Party shall:
  - (a) Create conditions to promote and encourage research which contributes to the conservation and sustainable use of biological diversity, particularly in developing countries, including through **simplified measures on access for non-commercial research purposes**, taking into account the need to address a change of intent for such research"

NON-COMMERCIAL BIOPROSPECTING

- Moorea Biocode Project (2006): UC Berkeley et. al., project to collect data (e.g. sequence DNA) on each species on the island
  - Developed ABS/PIC/MAT agreement with Government of French Polynesia
- Smithsonian DNA barcode project
- J. Craig Venter Institute sampling expeditions
- fewer than 15% of higher plant species are believed to have been examined for bioactivity



https://www.aber.ac.uk/en/news/archive/2013/10/title-141883-en.html

http://www.ncbi.nlm.nih.gov/genbank/

http://biocode.berkeley.edu/

DIGITIZATION OF SEQUENCE INFORMATION

- "Genomic science . . . is enabling researchers to "read" the genetic code of organisms from all branches of life . . . . Sequencing genomes has now become routine, giving rise to **thousands of genomes in the public databases.** In essence, scientists are digitizing biology by converting the A, C, T, and G's of the chemical makeup of DNA into 1's and 0's in a computer." J. Craig Venter Institute

NO NEED FOR TANGIBLE GENETIC STARTING MATERIAL

"Genetic engineers generally **extract a gene from an organism.** Then they might **modify** it or **put it in a different organism.** . . . It is a cut-and-paste operation, like writing a phrase by snipping the necessary words out of magazines and gluing them together in the proper order.

Gene synthesis, by contrast, is like **typing the phrase on a word processor.** Scientists specify the sequence of the desired gene and have it "**printed**" at the foundry. They can do this because the complete genome sequences of humans and many other species are available in **[online] databases.**" Andrew Pollack, New York Times

Market Players in Decoupling Design from Synthesis

(courtesy of Linda Kahl)

Computer-Aided Design (CAD)

GeneDesigner

TinkerCell

GenoCAD

GENOME COMPILER

CLOTHO

DNA synthesis and assembly

BlueHeron The Gene Synthesis Company

BIONEER Innovation • Value • Discovery

DNA 2.0

Desktop Genetics

GENEWIZ Solid science. Superior service.

Gen9

generay.com.cn GENEray Biotechnology

GenScript

IDT INTEGRATED DNA TECHNOLOGIES

life technologies

ShineGene

https://www.youtube.com/watch?v=nBmxkZEKCi0

UNIVERSITY of VIRGINIA SCHOOL OF LAW

NO NEED FOR TANGIBLE GENETIC STARTING MATERIAL

"Before the introduction of gene synthesis, Mr. Kuhn had to **isolate the genes from the virus itself, then put them into bacteria to have them produce the proteins.** Now he orders the genes from DNA2.0, a foundry.

"If we were starting this today**, I wouldn't even bother trying to get any of this from the natural source,**" Mr. Kuhn said. "**I would just order everything.**"" Andrew Pollack, New York Times

"DIGITAL BIOPIRACY"

"While biopiracy has conventionally meant the **physical removal** of a material from a community into private hands, synthetic biology enables ***digital biopiracy***, where the DNA of an organism is sequenced in situ, **uploaded to the internet as information**, and then transferred digitally to a DNA synthesizer so that copies can be rebuilt elsewhere. . . . most synthetic DNA sequences developed for synthetic biology are **near-copies of natural genetic code that has 'evolved' through computer models.**" ETC Group/Friends of the Earth 2010/2012

No need for MTA or PIC/ABS

DIGITAL BIOPIRACY?

- EPO Opposition filed December 2014

- "Members of the coalition of No Patents on Seeds! have filed an opposition against a European patent held by the US company Monsanto. **They are accusing Monsanto of biopiracy.** The patent EP2134870 was granted in February 2014 by the European Patent Office (EPO) and covers selecting soybean plants adapted to various climate zones for further breeding. For the patent, **Monsanto screened more than 250 plants from "exotic" species closely related to the soybean.** They were screened specifically for their genetic diversity regarding climate adaptation and the period of time needed to maturity and harvest. The plants were taken from both wild and cultivated species in Asia and Australia. In the patent Monsanto **claims the usage of hundreds of DNA sequences** originating from natural genetic diversity." https://www.bernedeclaration.ch/media/press-release/opposition_to_stop_monsanto_soybean_patent_biopiracy/

SIMILARITIES/DIFFERENCES TO ILLEGAL FILESHARING/DOWNLOADING OF COPYRIGHTED MATERIAL?

- Easier and cheaper to copy sequence info and create genes now
- Genetic resources not protected by IP (but may be national ABS/PIC/DOO obligations)
- Harder to detect improper use (DNA watermarking not foolproof)

COMMERCIAL VS. NON-COMMERCIAL RESEARCH AND SYNBIO

Sequences obtained from non-commercial research may be made available in databases and used (improperly) in commercial projects (copying easy, cheap).

Concerns about digital misappropriation may inhibit access to tangible genetic resources for non-commercial research (e.g., Indonesian 2014 moratorium on foreign biodiversity research)

SB OBLIGATIONS MAY COME FROM NATIONAL LEGISLATION, NOT NP ITSELF

Example: Brazil

- genetic heritage broadly defined as "*information* of genetic origin, contained in samples of all or part of a plant, fungal, microbial or animal species, in the form or molecules or substances originating in the metabolism of these living beings, and in extracts obtained from in situ conditions, . . ." Brazilian Provisional Act, No. 2,186-16, Title II, Art. 7, August 23, 2001.

Possible Future ABS/DOO Obligations

WORLD INTELLECTUAL PROPERTY ORGANIZATION (WIPO) INTERGOVERNMENTAL COMMITTEE (IGC) ON INTELLECTUAL PROPERTY AND GENETIC RESOURCES (GR), TRADITIONAL KNOWLEDGE (TK) AND TRADITIONAL CULTURAL EXPRESSIONS (TCES)

- Three draft texts
  - GR: Mandatory Disclosure of Origin (DOO) in patent applications
  - TK: Tiered protection (economic and moral rights)
  - TCEs: Tiered protection (economic and moral rights)

- May be combined into a single agreement (or reduced to two)

WHY IS IGC PROCESS TAKING SO LONG (15 YEARS AND COUNTING)?

- Simplification:
  - Demandeurs (mostly provider countries) want binding IP protection/ABS facilitation
  - Many Non-Demandeurs (mostly user countries) do not want an IP Agreement, nor a mandatory DOO requirement

DISCLOSURE OF GR ORIGIN (DOO) IN PATENT APPLICATIONS

Why being pushed:

"1. The fact that **patent claims** in various countries may incorporate biological and genetic material including life forms within their scope.

2. The conviction – widely held among developing countries and NGOs – that biodiversity and associated traditional knowledge have **tremendous economic potential.**

3. The belief, also shared by developing countries and NGOs, that this feature of the patent system enables corporations to **steal, misappropriate or unfairly free-ride** on genetic resources and associated traditional knowledge.

4. The ability of **modern intellectual property law** to protect the innovations produced by industries based mainly in the developed world and its ***in*ability to protect** adequately those in which the developing countries are relatively well endowed.

5. The perception that as a consequence of reasons 1 – 4, the **unequal distributions and concentrations of patent ownership and the unequal share of benefits** obtained from industrial use of biogenetic resources are closely related."

Queen Mary Institute Report (2004)

BURDEN? DISCLOSURE OF GR ORIGIN (DOO) IN PATENT APPLICATIONS

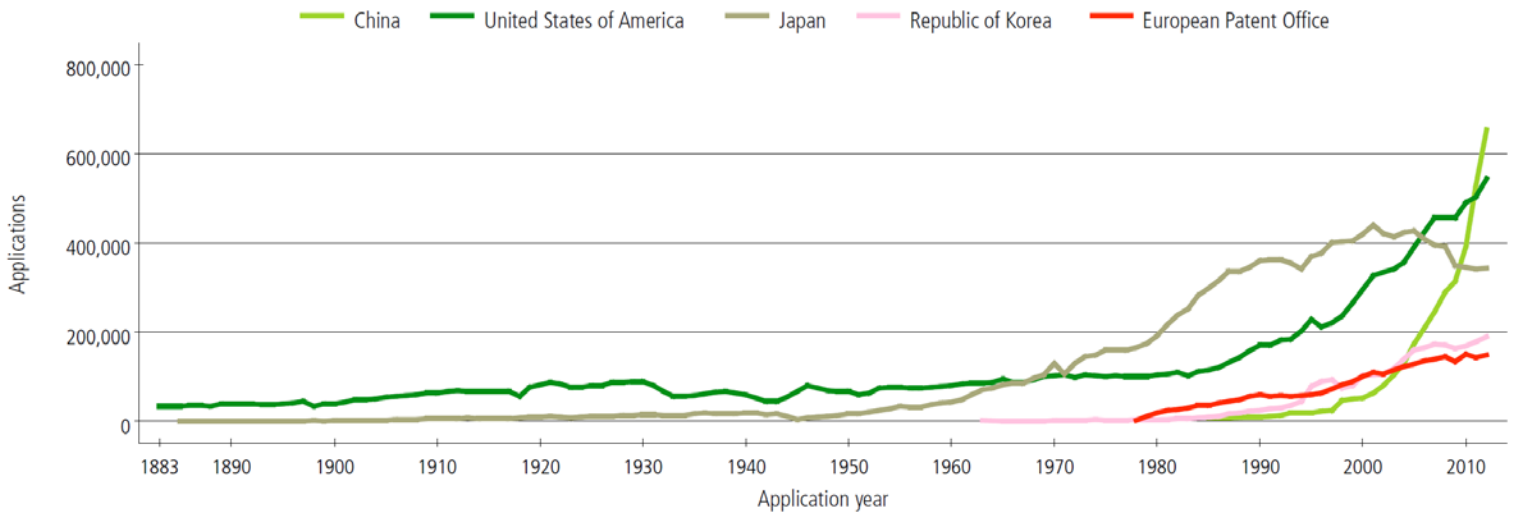
- DOO Requirements ALREADY in national laws of at least 20 countries (e.g., China, Brazil, India, Peru, EFTA States, Australia); IGC may simply harmonize requirement/add more
- Japan Bioindustry Organization, Biotechnology Industry Organization (BIO), other organizations have guidelines recommending PIC/ABS, various U.S. agencies as well (BUT BIO opposes DOO in patent applications)

THE NAGOYA PROTOCOL IS NOT AN IP TREATY, AND IS NOT UNDER WIPO, BUT

- Many WIPO members are party to CBD/NP
- Many WIPO members will be implementing CBD/NP
- IP office is a logical NP compliance checkpoint (with GR/TK disclosure of origin requirement for patent applicants) Two of four countries identifying checkpoints identified industrial property offices
- **Cross-border cooperation** against violations of CBD/NP-based GR/TK access and benefit sharing laws could affect grant/denial of patentsrights (e.g., draft Denmark law)

CHINA #1 DESTINATION FOR PATENT APPLICATIONS

Figure A.2.1.2 Trend in patent applications for the top five offices



Note: The top five offices were selected based on their 2012 totals.

Source: WIPO Statistics Database, October 2013

CHINESE PATENT ACT (3RD REVISION, EFFECTIVE 2009)

- "For an invention or creation completed based on genetic resources, the applicant shall give an **account in the patent application** documents of the **direct origin** and **ultimate origin** of the **genetic resources**. If the applicant is unable to give an account of the ultimate origin, it/he/she shall give the reason therefor." (Art. 26)

- " . . . If **genetic resources** are **obtained or used** in **violation of laws or administrative regulations** and an invention or creation is completed on the **basis of such genetic resources**, the **patent shall not be granted** therefor." (Art. 5)

CHINA'S DOO REQUIREMENT: NOT PLACING "UNDUE BURDEN" ON PATENT APPLICANTS

- China: currently receives more patent applications every year than any other country.
- Article 26.5 of the Chinese Patent Act (3rd Revision) requires patent applicants to disclose the origin of genetic resources used in creating a claimed invention.
- Between October 1, 2009 and June 30, 2013, genetic resource source forms were filed in 7,149 patent applications, most after the examiner requested submission of the form.
- Authors of China DOO study conclude that the new genetic resource disclosure requirements are **not placing an "undue burden"** on patent applicants (c.f., SIPO does get complaints)
- More than 20 countries already have GR/TK disclosure of origin requirements for patent applicants
- **Foreign applicants are already having to deal with such a requirement** if they are seeking patent protection in DOO countries such as China.

Qingkui Zhang and Dongcheng Pang, Chinese Patent Law and Protection for Genetic Resources 2014

MANDATORY DOO MAY INCREASE LEGAL CERTAINTY

"rather than cause uncertainty, new international treaty provisions addressing disclosure of origin requirements may help to **make more coherent** existing and future national laws regarding misappropriation, including their recognition and enforcement in other countries. At least such an instrument may **make existing uncertainties more transparent and predictable** with regard to national access and benefit-sharing and to intellectual property laws that are applicable to transboundary resource and information flows." Sarnoff & Correa, Analysis of Options for Implementing Disclosure of Origin Requirements in Intellectual Property Applications (2006)

EXAMPLE OF TRIPS COMPLIANT, WORKABLE DOO PROVISION (SWISS)

- "1. The patent application must contain information on the source:

  a. of the genetic resource to which the inventor or the patent applicant had access, provided the invention is directly based on this resource;

  b. of traditional knowledge of indigenous or local communities of genetic resources to which the inventor or the patent applicant had access, provided the invention is directly based on this knowledge.

  2. If the source is unknown to the inventor or the patent applicant, the patent applicant must confirm this in writing."
- Failure to comply prevents further processing of application
- But if patent issues and intentional deception discovered, penalized outside patent system (fines for perjury)

WIPO IGC AND NAGOYA PROTOCOL

ISSUE:

- Is there a DOO obligation with synthetic biology inventions using DNA sequences (no tangible GR used)?

- Not yet penetrated IGC discussions

- Preferable to address at international level

FURTHER FACILITATING DISCLOSURE OF ORIGIN AND BENEFIT SHARING

- Example JCVI language (from public database):
- "This genetic information downloaded from camera.calit2.net may be considered to be part of the genetic patrimony of Madagascar, the country from which the sample was obtained. Users of this information agree to: (1) acknowledge Madagascar as the country of origin in any publications where the genetic information is presented and (2) contact the CBD focal point identified on the CBD website (www.biodiv.orgdocinfo-centre.shtml) if they intend to use the genetic information for commercial purposes."

http://metagenomesonline.org/library-details?prefix=GCU

CONCLUSIONS

- Diverse and complex issues emerging with synthetic biology in relation to digital DNA, ABS, NP implementation, and IP treaties
- Issue: How to comply with spirit of CBD/NP ABS with digital DNA sequence information while not unduly burdening emerging synbio research
- Nagoya Protocol not designed to address digital misappropriation, will likely be addressed, if at all, under national law
- Need for study and action of SB/DOO interplay at the international level to minimize uncertainty, transaction costs
- Researchers should use due diligence to identify provenance of genetic material; likelihood of future digital DNA obligations uncertain

Questions???