

Patents and Synthetic Biology

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Overview

- 1) Synthetic biology technology
- 2) Claim examples
- 3) Patentability issues



Synthetic Biology

Technology Summarized by:

- 1) Parts
- 2) Pathways
- 3) Genomes
- 4) Systems

Rabinow & Bennett. “Synthetic biology: ethical ramifications 2009”
Systems and Synthetic Biology (2009) 3:99-108



Synthetic Biology

Parts

Single “part” or gene/enzyme to perform a particular function

Goals of this strategy:

- 1) To conceptualize and standardize the “parts” of biology to shift biology to a more engineering-like discipline
- 2) To reduce biological systems to their modular, additive parts that can be assembled (engineered) to perform new functions

Example: BioBricks™

- BioBricks™ Foundation at <http://bbf.openwetware.org/>
- BioBricks™ registry of parts at <http://partsregistry.org/>



Synthetic Biology

Pathways

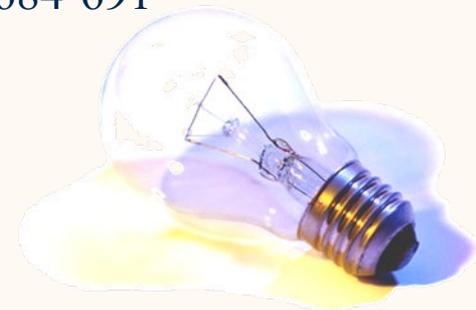
Several “parts” working together to perform an overall process

Goals of this strategy:

- 1) To additively use known parts, or engineered parts, to recreate efficient pathways/mechanisms in organisms to produce useful products, to newly degrade waste products, etc.
- 2) To develop organisms robust enough for commercial use -“microbial chemical factories”

Example: Keasling’s the drug artemisinin production

- In *S. cerevisiae* - *Nature* (2006) 440:940-943
- In *E. coli* - *Biotechnology and Bioengineering* (2006) 95(4):684-691



Synthetic Biology

Genomes

Designing, modifying, reconstructing, and synthesizing entire genomes

Goals of this strategy:

- 1) To determine what is a minimal genome
- 2) To fully synthesize a genome and insert it into a receptive “chassis” to make a fully-engineered organism
- 3) To produce designer genomes that provide new functions in a fully-engineered organism



Synthetic Biology

Genomes (cont)

Minimal genome examples:

- Mushegian & Koonin - *PNAS* (1996) 93:10268-10273
- Church - *Molecular Systems Biology* (Epub 2006) 2:45
- Venter - *Science* (1999) 286:2165-2169 &
PNAS (2006)103:425-430



Synthetic Biology

Genomes (cont)

Genome synthesis and insertion: Venter

- Genome transplantation between bacteria - *Science* (2007) 317:632-638
- Complete chemical synthesis of a genome - *Science* (2008) 319:1215-1220 and *PNAS* (2008) 105:20404-20409
- Creating bacteria with a genome that was produced in yeast – *Science* (2009) 325:1693-6



Synthetic Biology

Systems

Engineering an organism as a genetic biosensor
“system”

Example: Arkin & Anderson

- Genetic logic circuit – invasin expression linked to cellular cancer signals - *Journal of Molecular Biology* (2006) 355:619-627



Claim Examples

Parts

- Newly isolated or altered genes, enzymes and/or recombinant organisms containing them
- Example from artemisinin production



Claim Examples

Parts (cont)

Adapted from Claim 1. An isolated DNA encoding a polypeptide having the biological activity of **amorpha-4,11-diene synthase**, wherein the polypeptide encoded by the DNA has a sequence with at least 95% homology to SEQ ID NO: 1

Sample claim from U.S. Patent No. 7,541,172 to Wallaart et al.



Claim Examples

Pathways

- Unique combinations of genes, enzymes and/or recombinant organisms. Also methods of making old products using these combinations.
- Example from artemisinin production using a microbial “factory.”



Claim Examples

Pathways (cont)

Sample Claim. A genetically modified host cell that produces isopentenyl pyrophosphate via a mevalonate pathway, wherein the genetically modified host cell comprises:

a) a **heterologous** nucleic acid comprising a nucleotide sequence encoding amorphaadiene synthase; and

b) a **heterologous** nucleic acid comprising a nucleotide sequence encoding a cytochrome P450 enzyme that converts amorphadiene into amorpha-4-ene-11,12-epoxide,

wherein said cytochrome P450 enzyme is soluble in the cytosol of said genetically modified host cell.



Claim Examples

Pathways (cont)

Claim 17. A method for synthesizing amorpha-4,11-diene in a host microorganism, the method comprising culturing a transformed host microorganism ... comprising one or more nucleic acids heterologous to the host microorganism ..., wherein the one or more nucleic acids comprises:

- a) a nucleotide sequence encoding an **acetoacetyl-CoA thiolase**, wherein the acetoacetyl-CoA thiolase is present as the first step in the synthesis of IPP via the mevalonate pathway;
- b) a nucleotide sequence encoding a **farnesyl pyrophosphate synthase**; and
- c) a nucleotide sequence encoding **amorpha-4,11-diene synthase**, wherein said culturing ... results in production of amorpha-4,11-diene. (Emphasis added)

Sample claim from U.S. Patent No. 7,192,751 to Keasling *et al.*



Claim Examples

Genomes

- Minimal genomes, with particular genes omitted, are difficult to claim
- Methods of synthesis of large DNAs and genome transplantation are pioneering and claiming broad scope
- Generic products resulting from these pioneering methods (*i.e.*, synthetic organisms) are also claimed



Claim Examples

Genomes (cont)

Sample Claim. A set of **protein-coding genes** that provides the information required for growth and replication of a free-living organism under axenic conditions in a rich bacterial culture medium,

wherein the set **lacks** at least 35 of the 113 protein-coding genes listed in Table 7, or functional equivalents thereof,

wherein at least one of the genes in Table 14 is among the **lacking** genes;

wherein the set **comprises** between 355 and 383 of the 383 protein-coding genes listed in Table 2, or functional equivalents thereof, including at least one of the genes in Table 6;

and wherein the set **comprises** no more than 410 protein-coding genes.

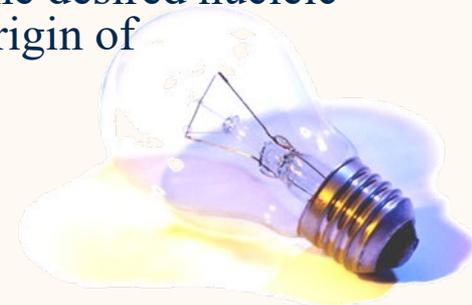


Claim Examples

Genomes (cont)

Sample Claim 1. A method for the synthesis of a desired nucleic acid molecule, comprising:

- a) providing a **plurality of cassettes**, each cassette containing the nucleotide sequence of a portion of the desired nucleic acid, wherein the cassettes contain overlapping portions of the nucleotide sequence of the desired nucleic acid molecule and wherein the cassettes, if combined according to the overlapping portions, provide the complete nucleotide sequence of the desired nucleic acid;
- b) **combining said cassettes *in vitro*** to obtain a plurality of **resulting subsets** wherein said subsets contain overlapping portions of the desired sequence and wherein the subsets, if assembled according to the overlapping portions, would provide the nucleotide sequence of the desired nucleic acid; and
- c) **assembling the subsets *in vivo*** in a host culture to obtain the desired nucleic acid molecule, wherein said assembly further includes an origin of replication.



Claim Examples

Genomes (cont)

Sample Claim 2. Isolated DNA molecules assembled by the method of claim 1.

Sample Claim 3. A host culture which comprises a DNA molecule assembled according to the method of claim 1.



Claim Examples

Genomes (cont)

Sample Claim 1. A method for making a synthetic cell, the method comprising: obtaining a genome that is not within a cell; and introducing the genome into a cell or cell-like system.

Sample Claim 16. A synthetic cell produced by obtaining a genome that is not within a cell, and introducing the genome into a cell or cell-like system.



Patentability Issues: Subject Matter Eligibility

35 U.S.C. 101

“Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.” (Emphasis added)

- *Diamond v. Chakrabarty* 447 U.S. 303, 206 USPQ 193 (1980)
- *Ex parte Allen* 2 USPQ2d 1425 (Bd. Pat. App. & Interf. 1987)
- Official Gazette Notice: Animals – Patentability 1077 O.G. 24, April 21, 1987
- MPEP 2105



Patentability Issues: Description and Enablement

35 U.S.C. 112, first paragraph

“The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.”



Patentability Issues: Written Description

- The claimed invention must be adequately described such that one skilled in the art would recognize Applicant was in possession of the claimed invention as a whole at the time of filing.

See Written Description Guidelines:

<http://www.uspto.gov/patents/resources/index.jsp>

- The “possession test” includes the following considerations:
 - a. Actual reduction to practice
 - b. Disclosure of drawings or structural chemical formulas
 - c. Sufficient relevant identifying characteristics, such as:
 - i. Complete structure
 - ii. Partial structure
 - iii. Physical and/or chemical properties
 - iv. Functional characteristics when coupled with a known or disclosed correlation between function and structure
 - d. Method of making the claimed invention
 - e. Level of skill and knowledge in the art
 - f. Predictability in the art



Patentability Issues: Enablement

- The claimed invention must be enabled so that any person skilled in the art can make and use the invention without undue experimentation.

See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) and MPEP 2164.

- The test for undue experimentation includes the following factors:
 - (A) The breadth of the claims;
 - (B) The nature of the invention;
 - (C) The state of the prior art;
 - (D) The level of one of ordinary skill;
 - (E) The level of predictability in the art;
 - (F) The amount of direction provided by the inventor;
 - (G) The existence of working examples; and
 - (H) The quantity of experimentation.



Patentability Issues: Enablement

Deposit Rules

37 C.F.R. 1.802 (b)

“Biological material need not be deposited unless access to such material is necessary for the satisfaction of the statutory requirements for patentability under 35 U.S.C. 112. If a deposit is necessary, it shall be acceptable if made in accordance with these regulations. Biological material need not be deposited, *inter alia*, if it is known and readily available to the public or can be made or isolated without undue experimentation.”



Patentability Issues: Prior Art

35 U.S.C. 102 (Novelty)

A person shall be entitled to a patent unless —

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

(e) the invention was described in — (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.



Patentability Issues: Prior Art

35 U.S.C. 103(a) (Non-Obviousness)

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
- 35 U.S.C. 103 is further understood in light of *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007)



In Closing

- Synthetic biology is not a new idea but has recently been developed to include whole genomes and organisms.
- With the issue of patentability of living organisms being decided, patentability typically revolves around novelty and non-obviousness in view of the naturally-occurring products on which the synthetic ones are based.



QUESTIONS?

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