



Patents and Synthetic Biology

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Overview

- 1) Synthetic biology – the technology
- 2) Patent claim examples
- 3) Patentability issues relating to the technology



Synthetic Biology

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 and artemisinin

- 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 (con't)

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 (con't)

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



Patent Claim Examples

Parts

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



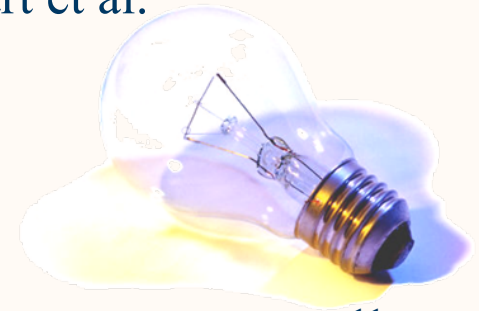
Patent Claim Examples

Parts (con't)

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 corresponding to the translation of a DNA exhibiting at least 95% homology to SEQ ID NO: 13.

(Emphasis added)

Sample claim from U.S. Patent 7,541,172 to Wallaart et al.



Patent 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”.



Patent Claim Examples

Pathways (con't)

Claim 11. 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 amorpha-4,11-diene into amorpha-4-ene-11,12-epoxide,

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

(Emphasis added)

Sample claim from U.S. Patent Application Publication
2008/0187983 to Keasling's group



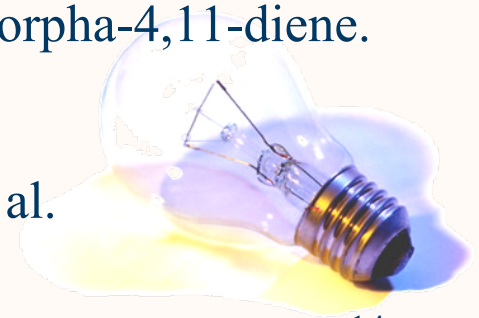
Patent Claim Examples

Pathways (con't)

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 7,192,751 to Keasling et al.



Patent 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



Patent Claim Examples

Genomes (con't)

Claim 1. 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 40 of the 101 protein-coding genes listed in Table 2, or functional equivalents thereof,

wherein at least one of the genes in Table 4 is among the lacking genes;

wherein the set comprises between 350 and 381 of the 381 protein-coding genes listed in Table 3, or functional equivalents thereof, including at least one of the genes in Table 5;

and wherein the set comprises no more than 450 protein-coding genes.

Sample claim from U.S. Patent Application Publication 2007/0122826 to Venter's group



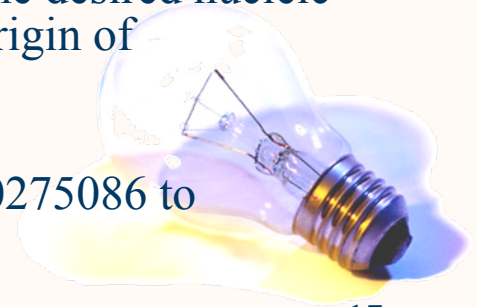
Patent Claim Examples

Genomes (con't)

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. (Emphasis added)

Sample claim from U.S. Patent Application Publication 2009/0275086 to Venter's group



Patent Claim Examples

Genomes (con't)

Claim 21. Isolated DNA molecules assembled by the method of claim 1.

Claim 23. A host culture which comprises a DNA molecule assembled according to the method of claim 1.

Sample claims from U.S. Patent Application Publication 2009/0275086 to Venter's group



Patent Claim Examples

Genomes (con't)

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.

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.

Sample claims from U.S. Patent Application Publication
2007/0269862 to Venter's group



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)

- Setting the stage for issues about patenting life forms

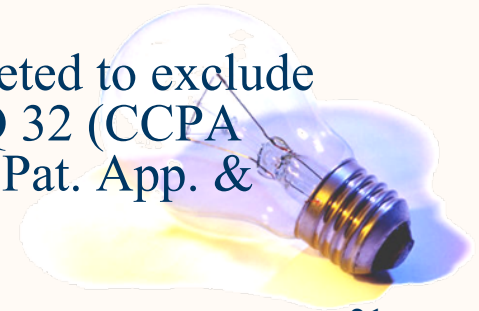


Patentability Issues: Subject Matter Eligibility

35 U.S.C. 161-164 Plant Patent Act

“Whoever invents or discovers and asexually reproduces any distinct and new variety of plant, including cultivated sports, mutants, hybrids, and newly found seedlings, other than a tuber propagated plant or a plant found in an uncultivated state, may obtain a patent therefor, subject to the conditions and requirements of this title.”

- Originally added to the United States Code to expressly provide for plants produced by artificial breeding techniques, but plants can still be claimed under 35 U.S.C. 101. See *Ex parte Hibberd*, 227 USPQ 443 (Bd. Pat. App. & Interf. 1985)
- The term “plant” here has specifically been interpreted to exclude bacteria. See *In re Arzberger*, 112 F. 2d 834, 46 USPQ 32 (CCPA 1940) and *Ex parte Hibberd*, 227 USPQ 443, 447 (Bd. Pat. App. & Interf. 1985). See also MPEP 1601.



Patentability Issues: Subject Matter Eligibility

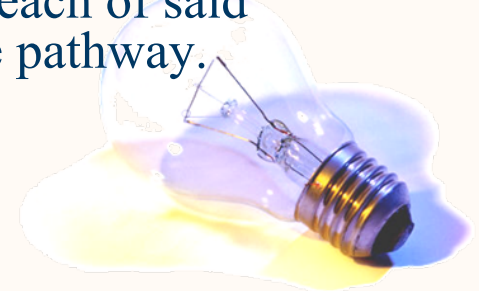
Diamond v. Chakrabarty

447 U.S. 303, 206 USPQ 193 (1980)

Genetically engineered microorganism, that is a living thing, was held as patentable subject matter under 35 U.S.C. 101.

“It is clear from the Supreme Court decision and opinion that the question of whether or not an invention embraces living matter is irrelevant to the issue of patentability. The test set down by the Court for patentable subject matter in this area is whether the living matter is the result of human intervention.” MPEP 2105

Sample Claim. A bacterium from the genus *Pseudomonas* containing therein at least two stable energy-generating plasmids, each of said plasmids providing a separate hydrocarbon degradative pathway.



Patentability Issues: Subject Matter Eligibility

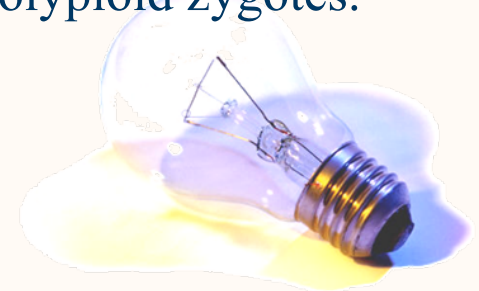
Ex parte Allen

2 USPQ2d 1425 (Bd. Pat. App. & Interf. 1987)

Rejected Claim 8. Polyploid Pacific oysters produced by the method of claim 1.

Depends from Claim 1. A method of inducing polyploidy in oysters, comprising:

separating oysters from one another such that male oysters are isolated from female oysters; inducing said oysters to spawn; controlling the temperature of eggs from said oysters; fertilizing said eggs with sperm to form zygotes; applying hydrostatic pressure to said zygotes at a predetermined intensity for a predetermined duration after a predetermined time following formation of said zygotes to induce polyploidy; and cultivating said polyploid zygotes.



Patentability Issues: Subject Matter Eligibility

Official Gazette Notice: Animals - Patentability

1077 O.G. 24, April 21, 1987

“The Patent and Trademark Office now considers nonnaturally occurring, non-human multicellular living organisms, including animals, to be patentable subject matter within the scope of 35 U.S.C. 101...

Accordingly, the Patent and Trademark Office is now examining claims directed to multicellular living organisms, including animals. To the extent that the claimed subject matter is directed to a non-human ‘nonnaturally occurring manufacture or composition of matter – a product of human ingenuity’ (Diamond v. Chakrabarty), such claims will not be rejected under 35 U.S.C. 101 as being directed to nonstatutory subject matter.”

See 1077 O.G. 24



Patentability Issues: Subject Matter Eligibility

MPEP 2105 – Patentable Subject Matter – Living Subject Matter

“If the broadest reasonable interpretation of the claimed invention as a whole encompasses a human being, then a rejection under 35 U.S.C. 101 must be made indicating that the claimed invention is directed to nonstatutory subject matter.”



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

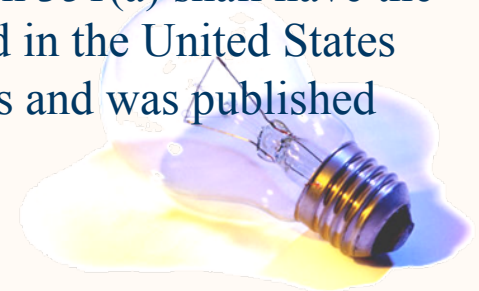
35 U.S.C. 102 (Novelty)

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.





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QUESTIONS?

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