



Project no. 043338

Project acronym: EMERGENCE

Project title: A foundation for Synthetic Biology in Europe

Instrument: NEST Pathfinder

Thematic Priority: Synthetic Biology

Deliverable 5.4_2: Status report on IPR discussion in synthetic biology, including recommendations

Due date of deliverable: 12, 36 Actual submission date: 36

Start date of project: 1.12.2006

Duration: 36 months

Organisation name of lead contractor for this deliverable: ETHZ, Geneart

Project co-funded by the European Commission within the Sixth Framework Programme (2002-2006)				
Dissemination Level				
PU	Public	X		
PP	Restricted to other programme participants (including the Commission Services)			
RE	Restricted to a group specified by the consortium (including the Commission Services)			
CO	Confidential, only for members of the consortium (including the Commission Services)			

This particular deliverable completes deliverable 5.4. The first part of this deliverable was delivered together with Deliverable 5.1_1, in which the IPR situation was analyzed as a result of an industry-academia workshop on the topic. Here, we provide a recommendation and an analysis of the SynBio patent landscape.

An IPR Strategy for Synthetic Biology in Europe – A Recommendation from the EMERGENCE Project

Introduction:

Synthetic biology intends to design biological systems. Such systems consist of multiple parts – currently, a limited number of parts, typically in the order of 10 per design, depending also on the definition of the term "part". However, in view of our rapidly increasing capacity to synthesize large segments of DNA *in vitro* and the advances in systems biology, it is easy to predict that we will soon design (or build by combinatorical approaches) much larger systems.

Traditionally, biotechnology patents focus on single genes. This is in line with the scope of traditional genetic engineering. However, if one single gene will be only one of a large number of parts in a biological design of ever increasing complexity, then it appears instrumental to ensure that the different parts in the system can a) at least be evaluated quickly in view of the Intellectual Property Rights (IPR) that are connected to them or b) the future users can be sure that the restrictions attached to the use of such parts do not prevent their use in a larger system.

On the other hand, patents enable the generation of revenues to an inventor and thus are an important incentive to valorize innovation.

Both options a) and b) are not trivial to implement and the balance between for example limiting patentability and providing incentives is difficult to achieve. The question of a suitable strategy for dealing with parts ownership has accompanied the synthetic biology community ever since the first Synthetic Biology conference at the MIT in 2004. The topic is also the focus of an FP7 EU-project (Synth-Ethics, <u>http://synthethics.eu/</u>), it has been treated by the European Group on Ethics in Science and New Technologies to the European Commission (opinion #25), and is the focus of a number of timely articles (eg Rai & Boyle, PLOS Biology 5:e58, Henkel & Maurer, Molecular Systems Biology 3:117, Rutz, EMBO Reports 10: S14).

Within the EMERGENCE project, the parts ownership topic was treated from a rather practical perspective. This practical perspective suggests that neither a pervasive "open source" model nor a traditional biotech-patent model might do the problem justice. Rather, the specific problems in synthetic biology might have to generate a solution *sui generis*.

A first attempt at such a tailor-made solution has already been made. The Biobricks Foundation currently explores the usefulness of a "Biobrick Contributor Agreement" (attached to this paper) with which a parts contributor rejects any claims of ownership when a part is delivered to a parts registry. This concept is certainly in agreement with point b) above, but of course is at odds with the idea to give incentive to valorization by IPR protection.

Instead, EMERGENCE proposes a different route. It is based on the observation that DNA sequencing on genome level has become a commodity. Current pyrosequencing-based DNA sequencers have a capacity of several times the *E. coli* genome per run while occupying the space of a typical laboratory bench-top device and requiring consumables in the order of 800 \in per operation (see the recently released Roche/454 GS Junior sequencer). Extrapolating from the exceptionally rapid development in DNA sequencing technology over the last 5 to 10 years, we feel it is save to predict that – at least on the level of bacteria and microorganisms or lower fungi with a genome size lower than 30 Mbp – the determination of the genomic DNA sequence will no longer be a decisive cost factor in any biotechnology project.

We argue that this rapid development justifies an insistence on behalf of the patent granting authority on clear demarcations of the claims connected to DNA sequences. Specifically, the authority should insist that

- a) if a DNA sequence is claimed, each claim has a clear identification as to which DNA sequence is attached to this claim and it is clear for which function it is claimed and the corresponding effect has been experimentally demonstrated
- b) if a biological system is claimed without connection to a DNA sequence (eg a strain resulting from a screening), then the system as such is protected, but its genes can be used without restrictions.

The goal of these two points is to make it possible to identify patent claims attached to DNA sequences by applying well-established DNA-sequence search algorithms. The underlying rational is that claims attached to DNA sequences would be much less of an obstacle if they were clearly identifiable. This requires on the one hand that functional claims that are not based on a DNA sequence do not protect a DNA sequence any longer (enforcing each applicant to clearly spell out the claimed sequences), and on the other hand, that a system is implemented which allows to precisely define which claim goes with exactly which sequence.

One obvious problem here is that many properties are not the result of single genes but rather of complex assemblies of genes. By limiting patentability to those genes for which a positive effect could be clearly demonstrated, the number of claims could be effectively limited.

We argue that this development provides a unique opportunity to influence the patenting process by making it a condition in future biotechnology patents to connect protected functionality to a specific DNA sequence in a way that connects claims directly to specific DNA sequences while at the same time preventing DNA sequences from being implicitly protected and thus from being invisible to the person that assembles a system.

Such a development would have the unique feature that it would make research on the IPR status of a specific part rather easy, because in order to find all claims related to a specific part, all that would be needed is a search in a suitable, properly linked DNA-sequence database, the algorithms for which are long established. Crucially, patent claims would need to be linked to DNA databases in an easy way, and this would of course require a number of novel regulations on how to write patents, which in turn would need to be controlled by patent authorities.

Furthermore, it would be important to keep such a system up to date, as the process from patent application to finally granted claims is a rather extensive one, in the process of which substantial re-writings can occur. By connecting sequences to each specific claim, it would become possible to easily update the database depending on whether a specific claim was granted or not and for which geographical region the ownership question is posed.

Furthermore, we would encourage the implementation of a "Biobrick Contributor Agreement" analogous to the proposal of the BioBricks Foundation, which provides a legal framework for a conscious decision of not owning parts upon submission to a registry.

It is clear that this concept will 1) be difficult to implement and 2) not protect against all possible scenarios. Nevertheless, we feel that such a development would remove many of the current obstacles for using multiple parts in the design of biological systems, simply because much of the insecurity around the ownership would be removed. This would be essential in particular for small and medium enterprises without the protection of in house IPR departments.

Therefore, we argue that this proposal should be investigated by the proper authorities at the EU commission to decide whether its merit justifies a legal initiative to this effect. We are well aware of the fact that the pervasiveness of ultra-cheap next generation sequencing technologies might just now not be large enough to justify immediate implementation. However, we are convinced that a sufficient pervasiveness will be achieved in the very near future (on the order of maybe two years), and thus it is feasible to start evaluating this proposal already in the near future.

Patent recherché on: IP landscape around "Synthetic Biology"

November, 2009, Christine Ludwig

Background information

Synthetic Biology is a very young emerging discipline that overlaps with biotechnology, software and electronics and combines knowledge from molecular biology, engineering, mathematics and physics to design and implement new cellular behaviours. As a consequence, the setting of strict technological boundaries to identify the relevant intellectual property landscape is rather difficult. Comprehensive patent search based on keywords, synonyms and patent classes requires a definition of how the term *Synthetic Biology* can be interpreted to identify those novel and foundational technologies that would be relevant for the *Synthetic Biology* field.

General problems:

Patenting too far "upstream" can create "patent thickets". Initial goals of *Synthetic Biology* are to produce components parts and fundamental processes. If IP protection issues for too much of these fundamental parts and processes, it may hinder both science and industrial applications.

1. Definition of Synthetic Biology to identify searchable key words and patent classes

source: http://en.wikipedia.org/wiki/Synthetic_biology

"The term *Synthetic Biology* has long been used to describe an approach to biology that attempts to integrate (or "synthesize") different areas of research in order to create a more holistic understanding of life. More recently the term has been used in a different way, signaling a new area of research that combines science and engineering in order to design and build ("synthesize") novel biological functions and systems."

In sum, *Synthetic Biology* comprises the design and fabrication of biological components and systems that do not already exist in nature as well as the re-design and production of already existing biological systems. Systems biology studies complex biological systems as integrated wholes, using tools of modelling, simulation, and comparison to experiment. The focus tends to be on natural systems, often with some (at least long term) medical significance.

Synthetic Biology studies how to build artificial biological systems for engineering applications, using many of the same tools and experimental techniques. But the work is fundamentally an engineering application of biological science, rather than an attempt to do more science. The focus is often on ways of taking parts of natural biological systems, characterizing and simplifying them, and using them as a component of a highly unnatural, engineered, biological system.

i) Keywords for Synthetic Biology patent search:

a) synonyms and related disciplines:

"synthetic biology" "systems biology" "systems engineering" "biotechnology" "biological systems" "living systems" "biosynthetic pathways" "biological/genetic engineering" "engineering applications"

b) application fields and tools:

"prokaryotes" "bacteria" "eukaryotes" "phage" "organisms" "enzymes" "genomics" "microbiology" "microorganism" "cell" "recombinant DNA technology" "promoters" "operons" "zinc finger proteins" "metabolite" "artificial cell/chromosome"

c) traits and methods:

"integrate" "synthesize" "redesign" "build" "construct" "express" "synthetic" "artificial" "interdisciplinary" combined with

"functions" "genetic/logic circuits" "modules" "gene switches" "networks" "traits" "gene regulation" "parts" "devices" "inverter"

d) specific terms:

"biofuel" "fluorinated pharmaceuticals" "ribosome switches" "bioenergetics" "bioremediation" "genome transplantation" "biobricks" "biosensors" "minimal cell/genome" "protocell"

Further definitions and associated terms can be found in review articles:

- A O'Malley M, Powell A, Davies JF, Calvert J. Knowledge-making distinctions in synthetic biology. Bioessays. 2008 Jan;30(1):57-65. PMID: 18081015

- Serrano L. Synthetic biology: promises and challenges. Mol Syst Biol. 2007;3:158. Epub 2007 Dec 18. PMID: 18091727

- Brownlee C. Michelle Chang: putting the pieces together with synthetic biology. ACS Chem Biol. 2007 Dec 21;2(12):772-4. No abstract available. PMID: 18154262

ii) relevant international patent classes (IPC), under which inventions directed to *Synthetic Biology* can be found:

- A01H New plants or processes for obtaining them
- C07H Sugars
- C07K Peptides
- C12N Microorganisms or enzymes
- C12Q Measuring or testig processes involving enzymes or micro-organisms
- C12P Fermentation or enzyme-using processes to synthesise a desired chemical compound or composition or to separate opticals isomers from a racemic mixture

iii) Patent filings in biotechnology

(source: European patent office in Nov. 2009: "Patenting Synthetic Biology? A Transatlantic perspective", Nov 2009")

Patenting activity in 2009: 3.051 applications worldwide (several members per family)

- 437 EPO applications
- 44 EPO patents granted



2. What would be patentable and/or copyrightable in Synthetic Biology?

a) Pathways:

- Unique combinations of genes, enzymes and/or recombinant organisms. Including methods of making known products using these combinations.

- Example from artemisinin production using a microbial "factory."

b) 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

c) novel biological functions, specific parts, sequences or uses are translated into:

- method claims: e.g. "method for synthesis of compound X..."

- product claims: e.g. nucleic acids, proteins, vectors, cells, micro-organisms

- use claims: e.g. "use of micro-organism Y for synthesis of ... "

- apparatus claims: "apparatus for synthesizing"

Examples:

- patents on fundamental ideas in synthetic biology:

US 5,914,891 (Univ. of Stanford): System and method for simulating operation of biochemical systems

WO08144192 (Craig Venter Inst./Synthetic Genomics): Methods of genome installation in a recipient host cell

WO07047148 (Craig Venter Inst./Synthetic Genomics): Minimal bacterial genome

This patent application by the Craig Venter group claiming a minimal genome for a living organism would also encompass any method of hydrogen or ethanol production that uses this minimal genome. This patent has received considerable media attention because it has been interpreted as a patent on the 'essence of *Synthetic Biology*

- patents on fundamental biological functions

US 6,774,222 (US Dep. of Health): Molecular computing elements, gates and flip-flops US 6,737,269 (Boston Univ.): Multi-state genetic oscillator

US 6,841,376 (Boston Univ.): Bistable genetic toggle switch US 6,828,140 (Boston Univ.): Adjustable threshold switch

patents on classes of biological molecules with a particular function:
US 6,903,185 (MIT): Poly zinc finger proteins with improved linkers
US 6,610,512 (Scripps Res. Inst.): Zinc finger binding domains for GNN
US 6,607,882 (Sangamo Biosciences): Regulation of endogenous gene expression in cells using zinc finger proteins

- patents on particular biological molecules:

e.g. patent on the sequence of a particular protein that senses light and transmits a signal into the cell etc.

3. Patent search "Synthetic Biology"

a) Selection of patent hits:

- keywords listed under 1.i) were rationally combined using Boolean operators and the respective search script was submitted to the patent family database PatBase licensed from the provider Minesoft Ltd. PatBase comprises more than 28 million patent families and bibliographic data from 65 countries. The keyword-based search yielded 196 patent families.

- A more specific search identified only those applications comprising the term "synthetic biology" either in the full text (91 hits) or in title and abstract (6 hits)

- The 196 hits which were statistically analysed for top patent classes, assignees, countries with most applications and filing behaviour over time.

b) Statistics:

i) Top 10 International Patent Classes (IPC), in which inventions directed to *Synthetic Biology* can be found:

The table indicates the number of the 196 found patent families categorized in a specific patent class. Usually, each patent family is assigned to different patent classes. Most of the patent families can be found in class C12N15 containing inventions directed to genetic engineering.

IPC	frequency	Definition
C12N15	105	Mutation or genetic engineering
C12N1	73	Micro-organisms, e.g. protozoa
C12P7	54	Preparation of oxygen-containing organic compounds
C12Q1	51	Measuring or testing processes involving enzymes or micro-organisms
C12N9	42	Enzymes, e.g. ligases
C07H21	40	Compounds containing two or more mononucleotide units having
		separate phosphate or polyphosphate groups linked by saccharide
		radicals of nucleoside groups, e.g. nucleic acids
C12N5	31	Undifferentiated human, animal or plant cells, e.g. cell lines
C07K14	24	Peptides having more than 20 amino acids
C12P19	22	Preparation of compounds containing saccharide radicals
C12P21	21	Preparation of peptides or proteins

ii) Top Assignees in Synthetic Biology:

The graph indicates the numbers of patent families filed by the listed Assignees



iii) Countries where most applications have been filed

The bar chart displays the number of patent family members filed in a specific country. Note that most of the 196 found patent families consist of several patent members filed in different countries



iv) years in which most patent families have been published



v) patent families containing the term "Synthetic Biology" in the title or abstract

Title: (WO09048971A) Systems and methods for producing synthetic microorganisms capable of translating proteins containing non-standard amino acids

Abstract: (WO09048971A)

The disclosed invention relates to the generation of host cells containing rare codons and/or absent tRNAs, and the use of orthogonal tRNA systems that can insert a non-standard amino acid into a growing peptide chain. This invention combined with the capacity to synthesize whole genomes has important implications in **synthetic biology**, as it allows the rewriting of the genetic code of existing or newly designed organisms.

First claim (WO09048971A):

1. A method expressing a protein containing one or more non-standard amino acids, comprising: providing a host organism with a genome, wherein the genome contains a gene for the protein, wherein the gene comprises one or more target codons; providing an orthogonal tRNA system comprising a non-standard tRNA, a non- standard aminoacyl-tRNA synthetase (NSAARS), and a non-standard amino acid, wherein the NSAARS charges the NStRNA with the non-standard amino acid; culturing the organism under conditions where the protein is expressed and the protein contains the non-standard amino acid.

	ication number	r ublication uate	Application number	Application date
WO	<u>)9048971 A1</u>	20090416	WO2008US79229	20081008

Assignee(s): SYNTHETIC GENOMICS INC

Title: (US2009047718A) Methods and compositions for producing solvents

Abstract: (US2009047718A)

Described herein are methods, compositions and **synthetic biology** approaches for solvent production, including but not limited to butanol production. Described herein are recombinant bacteria and yeast strains which may be used in production of a solvent, including but not limited to butanol, from lignocellulosic and other plant-based feedstocks. Described herein are methods of producing solvents, including but not limited to butanol production but anol, using bacteria and yeast strains. Described herein are methods of producing organisms that display highly efficient butanol production.

First claim (US2009047718A):

1. A first recombinant solventogenic organism comprising an altered expression of at least one gene involved in a solvent production pathway relative to the expression in the first organism strain prior to its transformation, wherein the expression of the gene is altered in a corresponding manner in a hyper-butanol producing strain of a second organism, andfurther wherein said hyper-butanol producing strain of the second organism produces butanol more efficiently than a second organism strain prior to its transformation.

Family:	Publication number	Publication date	Application number	Application date
	AU2008254423 AA	20081127	AU20080254423	20080519
	CA2691998 AA	20081127	CA20082691998	20080519
	<u>US2009047718 AA</u>	20090219	US20080154027	20080519
	WO08144060 A2	20081127	WO2008US06466	20080519
	WO08144060 A3	20090625	WO2008US06466	20080519

Assignee(s): (std):

ADVANCED BIOFUELS INC ; TETRAVITAE BIOSCIENCE INC

Title: (WO08089983A) TWO-COMPONENT SYSTEM FOR PROGRAMMING A BACTERIAL MEMBRANE

Abstract:

The present invention relates to a modified bacterium with a two-component system, wherein an outside signal (3) strikes the bacterial cell membrane. The outside signal (3) is received by a first component (1) of the twocomponent system inside the bacterium, the reception of the outside signal (3) brings about a change of a second component (2) of the two-component signal, the second component (2) in the bacterium brings about a change in the proteome and/or transcriptom (4), the change (4) modifies the bacterial cell membrane, and the modification of the bacterial cell membrane is stored in a medium outside the bacterium. In addition, the invention comprises the use of the bacterium in nanotechnology, **synthetic biology**, for the production of chips, for screening methods and/or for biochemical assays, and further comprises a programmable, bacterial cell membrane, which can be produced from a bacterium according to the invention by isolating the cell membrane from the bacterium.

First claim:

1. Modifiziertes Bakterium mit einem Zwei-Komponentensystem, wobei 5 - ein aeusseres Signal (3) auf die bakterielle Zellmembran trifft; das aeussere Signal (3) durch eine erste Komponente (1) des Zwei-Komponentensystems innerhalb des Bakteriums empfangen wird; das Empfangen des aeusseren Signals (3) eine Veraenderung einer zweiten Komponente (2) des Zwei-Komponentensystems bewirkt; '(R) - die zweite Komponente (2) in dem Bakterium eine Veraenderung im Proteom und/oder Transkriptom (4) bewirkt; die Veraenderung die bakterielle Zellmembran veraendert; und die Veraenderung der bakteriellen Zellmembran in einem Medium ausserhalb des Bakteriums gespeichert wird. 15

Family:	Publication number	Publication date	Application number	Application date	
	<u>DE102007003577 A1</u>	20080807	DE200710003577	20070124	
	WO08089983 A1	20080731	WO2008EP00545	20080124	

Assignee(s): (std): UNIV WUERZBURG J MAXIMILIANS

Title: (US2009061520A) Synthetic biology vectors

Abstract: (US2009061520A)

The present invention provides compositions, methods and kits for generating synthetic genetic circuits in biological systems. In particular, the present invention provides vectors, reagents and methods of their use in constructing synthetic genetic circuits in bacteria.

First claim (US2009061520A):

1. A method for creating a synthetic genetic circuit comprising:a) providing:i) a host cell,ii) a first vector wherein said first vector comprises a selectable marker sequence and wherein said vector is stably integrated into said host cell genome,iii) a second vector comprising a different selectable marker sequence, genetic elements of interest, and first and second homologous sequence that are each homologous to a portion of said selectable marker sequence in said first vector, wherein said first homologous sequence is located 3' of said different selectable marker sequence and said genetic elements of interest, and second homologous sequence is located 5' of said different selectable marker sequence and said genetic elements of interest, andb) applying said second vector to said host cell such that recombination occurs between said selectable marker sequence in said first vector and said genetic elements of said selectable marker sequence and said genetic elements of said different selectable marker sequence is located 5' of said different selectable marker sequence sequence is located 5' of said different selectable marker sequence and said genetic elements of interest, andb) applying said second vector to said host cell such that recombination occurs between said selectable marker sequence in said first vector and said genetic elements of interest at a location within said selectable marker sequence of said host cell's genome, thereby generating a synthetic genetic circuit.

-		i ubiicution dute	Application number	Application date
<u>US2</u>	2009061520 AA	20090305	US20070935164	20071105

Assignee(s): (std): UNIV MICHIGAN

Title: (US2008286871) Modular genomes for synthetic biology and metabolic engineering

Abstract: (US2008286871)

The invention provides methods and compositions for assembling a modular replacement genome in a host microorganism. After such assembly, the host organism's genome is inactivated or ablated to permit full control of host cellular functions by the replacement genome. A modular replacement genome comprises an assembly of nucleic acid fragments, or segments, derived from one or more natural organisms or from synthetic polynucleotides or from a combination of both. Such an assembly, or set, of segments making up a replacement genome comprises a substantially complete set of genes and regulatory elements for carrying out minimal life functions under predefined culture conditions. The invention provides modular genomes having modules that are amenable to facile replacement, deletion, and/or additions. Such modules may be synthetic polynucleotides and may be designed for controlling gene content, excluding of genes that encode inhibitors or otherwise undesirable competing enzymes that divert a host cell from desired metabolic/ synthetic processes; modifying codon usage to maximize or minimize protein production; modifying regulatory elements, including promoters, enhancers, repressors, activator, or the like, to modulate gene expression; balancing enzymatic and transport activities to optimize fluxes of substrates, intermediates, and products in metabolic pathways, and like objectives.

First claim (US2008286871A):

1. A method of assembling a replacement genome in a host organism having a host genome, the method comprising the steps of:(a) providing a plurality of segments that cover a replacement genome, each segment being associated with one or more recombination elements, wherein at least one of such recombination elements comprises a portion of the segment;(b) transforming or co-transforming the host organism with one or

more segments to form a precursor genome, the precursor genome having a region homologous to the portion of the at least one recombination element, and the precursor genome being a recombinant of the one or more segments or a recombinant of a prior precursor genome and the one or more segments, such recombinant being formed by recombination of the recombination elements associated with the one or more segments, wherein such recombination includes recombination of the portion of the at least one recombination element and the corresponding homologous region of the precursor genome;(c) repeating step (b) with segments of a predetermined ordering until the replacement genome is formed; and(d) removing the host genome.

CA2625262 AA20071004CA2006262526220061012EP1948803 A220080730EP2006084943820061012JP2009524406 T220090702JP20080535131T20061012US2007087366 AA20070419US2006054673520061012US2007243617 AA20071018US2006054660920061012US2008286871 AA20081120US2007098684320071127WO07085906 A220070802WO2006IB0413220061012WO07085906 A320071129WO2006IB0413220061012WO07110695 A220071004WO2006IB0370620061012WO07110695 A320080313WO2006IB0370620061012	Family:	Publication number	Publication date	Application number	Application date
EP1948803 A220080730EP2006084943820061012JP2009524406 T220090702JP20080535131T20061012US2007087366 AA20070419US2006054673520061012US2007243617 AA20071018US2006054660920061012US2008286871 AA20081120US2007098684320071127WO07085906 A220070802WO2006IB0413220061012WO07085906 A320071129WO2006IB0413220061012WO07110695 A220071004WO2006IB0370620061012WO07110695 A320080313WO2006IB0370620061012		<u>CA2625262 AA</u>	20071004	CA20062625262	20061012
JP2009524406 T220090702JP20080535131T20061012US2007087366 AA20070419US2006054673520061012US2007243617 AA20071018US2006054660920061012US2008286871 AA20081120US2007098684320071127WO07085906 A220070802WO2006IB0413220061012WO07085906 A320071129WO2006IB0413220061012WO07110695 A220071004WO2006IB0370620061012WO07110695 A320080313WO2006IB0370620061012		EP1948803 A2	20080730	EP20060849438	20061012
US2007087366 AA US2007243617 AA20070419US2006054673520061012US2007243617 AA20071018US2006054660920061012US2008286871 AA20081120US2007098684320071127WO07085906 A220070802WO2006IB0413220061012WO07085906 A320071129WO2006IB0413220061012WO07110695 A220071004WO2006IB0370620061012WO07110695 A320080313WO2006IB0370620061012		JP2009524406 T2	20090702	JP20080535131T	20061012
US2007243617 AA20071018US2006054660920061012US2008286871 AA20081120US2007098684320071127WO07085906 A220070802WO2006IB0413220061012WO07085906 A320071129WO2006IB0413220061012WO07110695 A220071004WO2006IB0370620061012WO07110695 A320080313WO2006IB0370620061012		<u>US2007087366 AA</u>	20070419	US20060546735	20061012
US2008286871 AA20081120US2007098684320071127WO07085906 A220070802WO2006IB0413220061012WO07085906 A320071129WO2006IB0413220061012WO07110695 A220071004WO2006IB0370620061012WO07110695 A320080313WO2006IB0370620061012		<u>US2007243617 AA</u>	20071018	US20060546609	20061012
WO07085906 A220070802WO2006IB0413220061012WO07085906 A320071129WO2006IB0413220061012WO07110695 A220071004WO2006IB0370620061012WO07110695 A320080313WO2006IB0370620061012		<u>US2008286871 AA</u>	20081120	US20070986843	20071127
WO07085906 A320071129WO2006IB0413220061012WO07110695 A220071004WO2006IB0370620061012WO07110695 A320080313WO2006IB0370620061012		<u>WO07085906 A2</u>	20070802	WO2006IB04132	20061012
WO07110695 A220071004WO2006IB0370620061012WO07110695 A320080313WO2006IB0370620061012		WO07085906 A3	20071129	WO2006IB04132	20061012
WO07110695 A3 20080313 WO2006IB03706 20061012		<u>WO07110695 A2</u>	20071004	WO2006IB03706	20061012
		<u>WO07110695 A3</u>	20080313	WO2006IB03706	20061012

Assignee(s): (std): BC CANCER AGENCY

Title: (US2007031942A) Making nucleic acid sequences in parallel and use

Abstract: (US2007031942A)

The present invention relates generally to the fields of genomics, **synthetic biology** and genetic engineering. More particularly, the present invention concerns the methods that enable parallel multiplex ligation and amplification on surface for making assemblies of nucleic acids of various biological applications and for analysis of biological samples such as DNA, RNA, and proteins.

First claim (US2007031942A):

1. A method for producing polymers of nucleic acids comprising: (a) placing two or more different capture probes on a solid surface (b) applying an oligonucleotide mixture to the solid surface wherein the oligonucleotide mixture comprises two or more oligonucleotides; (c) hybridizing the oligonucleotide mixture to the capture probes, forming hybridizing duplexes containing nicking and/or gapping sites; (d) joining the nicking and gapping sites contained in the hybridizing duplex using ligation thereby producing polymers of nucleic acids.

Family:	Publication number	Publication date	Application number	Application date
	<u>CN101133166 A</u>	20080227	CN200680006662	20060301
	<u>US2007031942 AA</u>	20070208	US20060365980	20060301
	<u>US7544793 BB</u>	20090609	US20060365980	20060301
	WO07040592 A1	20070412	WO2006US07249	20060301
	<u>WO07040592 C1</u>	20080821	WO2006US07249	20060301
Assignee(s): (std):	GAO XIAOLIAN ; SH	ENG NIJING ; XIAI	LOIAN GAO ; ZHANG	XIAOLIIN ; ZHU QI
<u> </u>	ZHOU XIAOCHUAN	ZHENG XIAOLIN	; ZHANG XIAOLIN ; S	SHENG NUING ;

SHENG NILING ; GAO XIALOIAN ; GAO XIAIOIAN

The BioBrick[™] Public Agreement

DRAFT Version 1a

January 2010

For public distribution and comment

Please send any comments or feedback to Drew Endy & David Grewal c/o

endy@biobricks.org

grewal@biobricks.org

The BioBrick[™] Contributor Agreement

DRAFT Version 1a (January 2010)

The "Materials" are the particular standardized genetic material(s), their uses, and any associated sequence or functional information described as follows:

Please include the BioBrick part number(s) and any applicable BioBrickTM Standard(s), if appropriate:

Contributor may list and submit as many different Materials as Contributor wishes under this Contributor Agreement.

The "Contributor" is the person, company, institution, or other entity submitting the Materials and who is entering into this Agreement.

Name, address, and contact information of Contributor:

Person entering into this Contributor Agreement under authority of Contributor (if different from above):

Should Users attribute the Materials to Contributor as provided in Paragraph 5(b) below?

__Yes ___No

If attribution to Contributor is requested, please specify how the attribution should read:

(may include name of institution or company, principal researchers, etc.)

Preface

The BioBricks Foundation, Inc. (the "Foundation") was established to foster and advance innovation, research, standardization, and education in synthetic biology through the open design, construction, distribution, understanding, and use of BioBrick[™] compatible parts, namely standardized genetic materials and associated functional information, in ways that benefit the world. The Foundation believes that a free and easy-to-use legal framework for sharing and making use of engineered genetic materials underlies and serves these goals. Some such genetic materials may be subject to patents; some will not be. The patent-related provisions in this Contributor Agreement may or may not apply to the Materials (as defined above). 1. <u>Authority</u>. Contributor represents and warrants that Contributor has the right to enter this Contributor Agreement as a Contributor. By clicking "Agree" above in this BioBrickTM Contributor Agreement (the "Contributor Agreement") with respect to the Materials that Contributor is making available, Contributor agrees to the terms of this Contributor Agreement and permits those who receive the Materials under a BioBricks User Agreement ("Users") to use the Materials as provided therein.

2. <u>BioBrickTM</u> Identification Tag. Contributor agrees that the Materials may be modified to include a BioBrickTM identification tag and in order to inform potential users and contributors of the BioBricks framework to include the _____.org URL.

3. <u>Rights, Obligations, and Non-Assertion</u>.

(a) If any portions of the Materials (including but not limited to a nucleic acid sequence within the Materials), any composition containing the Materials, and/or any use of the Materials are protected by any patent, patent application, copyright, data right, or other proprietary right belonging to Contributor, Contributor irrevocably agrees in connection with the Materials: not to assert or threaten to assert such patents or property rights; not to initiate International Trade Commission proceedings; not to threaten assertion of any rights that may be granted through issuance of a patent application; not to invite to license; and not to enforce such proprietary rights in the Materials as provided in any manner against or otherwise adverse to the Foundation or Users (including a User's manufacturers, distributors, customers, or anyone else acting under User's authority or control), materials repositories, and/or materials libraries.

(b) The terms of this Contributor Agreement are binding upon both Contributor and User. Contributor acknowledges having read and understood the applicable BioBrick User Agreement.

4. <u>Intellectual Property Rights</u>. By filling in the information box below (or indicating "None" below), Contributor represents that, to the best of Contributor's knowledge: (i) there are issued patents or pending patent applications, copyrights, or data rights owned by the Contributor or another party that protect any portion of the Materials (including but not limited to a nucleic acid sequence within the Materials), any composition containing the Materials, or their use; and (ii) the Materials, or portions thereof, including but not limited to a nucleic acid sequence within the Materials, any compositions containing the Materials, and/or any use of the Materials, may be protected by any patent, patent application, or other intellectual property right belonging to the Contributor.

Patent No. or Application No.	Copyrights or Data Rights

By indicating "None," Contributor represents that, to the best of Contributor's knowledge, there are no issued patents, currently pending patent applications, copyrights, or data rights that protect the Materials, in whole or in part, contributed under this Contributor Agreement, including a nucleic acid sequence within the Materials, a composition containing the Materials, or their use:

None:

This Contributor Agreement covers only the Materials described herein and no others unless specifically covered by a new Contributor Agreement.

5. <u>Attribution</u>.

(a) Users of the Materials who commercialize and distribute the Materials in either their original form or a modified form are asked to agree to attribute the provision of the Materials under this Contributor Agreement by conspicuously including the BioBrick[™] Public Agreements logo in packaging, product inserts, websites, or other public displays. In order to ensure the quality and integrity of the Foundation's activities, the Foundation has the rights to that logo and all goodwill derived from its use.

(b) If Contributor requests attribution, Users will be required to use reasonable efforts to attribute the Materials to Contributor in the manner described [at _____] when the User describes the Materials in packaging or product inserts, publications, other public displays, or grant-related materials.

6. <u>Protocols</u>. Contributor is encouraged to ensure that the Materials provided under this Contributor Agreement are compatible with one or more of the BioBrickTM protocols and standards and that any applicable standards are so noted. Contributors and Users are, however, in no way restricted from adopting any other protocol or standard.

7. <u>Applicable Laws</u>. Contributor is obligated to comply with laws and regulations applicable to the Materials, including laws and regulations governing export control and safety. Because laws and regulations vary around the world and change frequently, the Foundation cannot advise Contributor concerning compliance with any applicable laws or regulations. The existence of this Contributor Agreement does not indicate that the contribution, making available, distribution, or use of the Materials is permitted by applicable law.

8. <u>Fees and Other Undertakings</u>. Contributor understands that no fees will be charged by Contributor or the Foundation to a User for the Materials. However, appropriate and nominal fees may be charged to the User for the manufacture and shipping of the Materials and additional fees may be charged for additional services or consulting requested by a User. Further, nothing in this Contributor Agreement shall preclude Contributor from voluntarily entering into a separate agreement with User or another party regarding the Materials that may vary from or supersede the terms of this Contributor Agreement or the User Agreement. Any such separate agreement, however, shall not diminish or derogate from the rights of the User in the Materials as provided under this Contributor Agreement.

9. <u>No Warranty</u>. NEITHER THE FOUNDATION, ANY MATERIALS REPOSITORY, MATERIALS LIBRARY, OR MATERIALS MANUFACTURER, NOR ANY OTHER PARTY MAKES ANY WARRANTY OR REPRESENTATION, EXPRESSED OR IMPLIED, WITH RESPECT TO THE MATERIALS, WHICH ARE PROVIDED "AS IS" EXCEPT WHERE SPECIFICALLY PROVIDED UNDER THIS BIOBRICK CONTRIBUTOR AGREEMENT. ALL OTHER WARRANTIES ARE EXPRESSLY EXCLUDED AND DISCLAIMED TO THE MAXIMUM EXTENT PERMITTED BY APPLICABLE LAW, INCLUDING WITHOUT LIMITATION IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, AND ANY WARRANTIES ARISING BY STATUTE OR OTHERWISE IN LAW OR FROM COURSE OF DEALING, COURSE OF PERFORMANCE, OR USE OF TRADE. ANY STATEMENTS OR REPRESENTATIONS MADE BY ANY OTHER PERSON OR ENTITY ARE VOID.

10. <u>Limitation of Liability</u>. IN NO EVENT WILL USERS, THE FOUNDATION, ANY MATERIALS LIBRARY, ANY MATERIALS REPOSITORY, OR ANY OTHER PARTY WHO HAS BEEN INVOLVED IN THE DESIGN, CONSTRUCTION, PRODUCTION, DISTRIBUTION, OR ANY OTHER ACTIVITY INVOLVING THE MATERIALS BE LIABLE TO CONTRIBUTOR OR ANY OTHER PARTY FOR ANY SPECIAL, INDIRECT, INCIDENTAL, RELIANCE, EXEMPLARY, OR CONSEQUENTIAL DAMAGES, INCLUDING LOSS OF DATA OR PROFITS, OR FOR INABILITY TO USE THE MATERIALS, EVEN IF THE USERS, THE FOUNDATION, OR SUCH OTHER PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES.

11. <u>Warranties and Representations</u>. Contributor provides no representations or warranties of any kind in the Materials, implied or express, except the promises of authority in Paragraph 1, non-assertion in Paragraph 3, and intellectual property in Paragraph 4.

12. <u>Interpretation of this Contributor Agreement</u>. This Contributor Agreement shall be interpreted under the laws of the Commonwealth of Massachusetts and the United States of America.

13. <u>Applicability</u>. This Contributor Agreement is binding upon Contributor and its, her, or his heirs, successors, administrators, and assigns.

The BioBrickTM User Agreement

DRAFT Version 1a (January 2010)

The "User" is the person who may request and use the Materials, or the company, institution, or other entity on whose behalf User is authorized to act.

Name, Address, Contact Information of User:

Person entering into this User Agreement under authority of User:

Preface

The BioBricks Foundation, Inc. (the "Foundation") was established to foster and advance innovation, research, standardization, and education in synthetic biology through the open design, construction, distribution, understanding, and use of BioBrickTM compatible parts, namely standardized genetic materials and associated functional information, in ways that benefit the world. The Foundation believes that a free and easy-to-use legal framework for sharing and making use of engineered genetic materials underlies and serves these goals. Some such genetic materials may be subject to patents; some will not be. The patent-related provisions in this User Agreement may or may not apply to the Materials (as defined by one or more Contributors in their respective Contributor Agreements).

1. <u>Authority</u>. By clicking "Agreed" above User agrees to the terms of this User Agreement and shall therefore have the right to use the Materials insofar as the Materials are within the public domain or the Contributors have promised not to assert any of the Contributors' proprietary rights against User by way of the applicable Contributor Agreements. This User Agreement applies to all Materials that User may receive via one or more Contributors under their BioBricks Contributor Agreements and the terms of this User Agreement are binding upon both User and Contributor.

2. <u>Use of the Materials</u>.

(a) User acknowledges that the Contributor is asked to represent and warrant if, to the best of the Contributor's knowledge: there are any issued patents or pending patent applications, copyrights, or data rights owned by the Contributor or another party that protect any portion of the Materials (including but not limited to a nucleic acid sequence within the Materials), any composition containing the Materials, or their use including but not limited to a nucleic acid sequence within the Materials, any compositions containing the Materials, and/or any use of the Materials, and that the Contributor, in connection with the Materials, will not assert or threaten to assert such patent; will not initiate International Trade Commission proceedings; will not threaten assertion of any rights that may be granted through issuance of a patent application; will not invite license rights to the Materials; and will not enforce any such intellectual property rights in the Materials in any manner against either the Foundation or Users (including a User's manufacturers, distributors, customers, or anyone else acting under User's authority or control). (b) This User Agreement and the applicable Contributor Agreements are specifically limited to the Materials described in the particular Contributor Agreements.

(c) User acknowledges having read and understood the applicable BioBrickTM Contributor Agreement(s) relating to the Materials (the "Contributor Agreement(s)").

(d) Users are encouraged to use, improve, and, as needed, develop BioBrick[™] protocols and standards, and to note any such standards in the distribution or redistribution of Materials. Users and Contributors are in no way restricted from adopting any other protocol or standard.

3. <u>Identification and Attribution</u>.

(a) As to identification tags: User agrees not to remove or alter any BioBrickTM identification tag or data included in the Materials and in order to inform potential users and contributors of the BioBricks framework not to remove or alter the _____.org URL.

(b) As to use of the BioBrick Agreements: If User makes available, commercializes, or otherwise distributes the Materials, as above, in either their original form or a modified form, User shall attribute use of the BioBrick Agreements to the Foundation by using reasonable efforts to conspicuously include the BioBrick[™] Public Agreements logo in all packaging or product inserts, publications, and grant-related materials related to the Materials and modifications of the Materials. In order to ensure the quality and integrity of the Foundation's activities, the Foundation owns that logo and all goodwill derived from its use.

(c) As to attributing Contributors: If Contributor has requested attribution under the Contributor Agreement, User will make reasonable efforts to recognize the Contributor as specified in Paragraph 5 of the Contributor Agreement when User makes available, commercializes, or otherwise distributes the Materials, including any descriptions of the Materials in packaging, product inserts, websites, publications, or other public displays.

4. <u>Applicable Laws</u>. User is obliged to comply with laws and regulations applicable to the Materials, including laws and regulations governing export control and safety. User will also respect the valid property rights of others in the Materials. Because laws and regulations vary around the world and change frequently, the Foundation cannot advise User concerning compliance with any applicable laws or regulations, nor can the Foundation make any determination regarding intellectual property rights. The existence of this User Agreement does not indicate that the contribution, distribution, or use of the Materials is permitted by applicable law.

5. <u>No Harmful Uses</u>. User will refrain from using the Materials in connection with any intentionally harmful, negligent, or unsafe uses.

6. <u>Fees and Other Undertakings</u>. User understands that no fees will be charged for providing access to or use of the Materials. However, appropriate and nominal fees may be charged to User for the manufacture and shipping of the Materials and additional fees may be charged for additional services or consulting requested by User. Further, nothing in this User

Agreement shall preclude User and any Contributors from voluntarily entering into a separate agreement with User or another party regarding the Materials that may vary from or supersede the terms of this User Agreement or the Contributor Agreement. Any such separate agreement, however, shall not diminish or derogate from the rights of the User in the Materials as provided under this User Agreement.

No Warranty. NEITHER THE CONTRIBUTOR, THE FOUNDATION, ANY 7. REPOSITORY, MATERIALS LIBRARY, MATERIALS OR MATERIALS MANUFACTURER, NOR ANY OTHER PARTY MAKES ANY WARRANTY OR REPRESENTATION, EXPRESSED OR IMPLIED, WITH RESPECT TO THE MATERIALS, WHICH ARE PROVIDED "AS IS" EXCEPT WHERE SPECIFICALLY PROVIDED UNDER THE BIOBRICK CONTRIBUTOR AGREEMENT. ALL OTHER WARRANTIES ARE EXPRESSLY EXCLUDED AND DISCLAIMED TO THE MAXIMUM EXTENT PERMITTED BY APPLICABLE LAW, INCLUDING WITHOUT LIMITATION IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, AND ANY WARRANTIES ARISING BY STATUTE OR OTHERWISE IN LAW OR FROM COURSE OF DEALING, COURSE OF PERFORMANCE, OR USE OF TRADE. ANY STATEMENTS OR REPRESENTATIONS MADE BY ANY OTHER PERSON OR ENTITY ARE VOID. USER ASSUMES ALL RISK AS TO THE QUALITY, FUNCTION, AND PERFORMANCE OF THE MATERIALS AND ALL RISK FOR ANY CONSEQUENCE OF USING, COMMERCIALIZING, OR REDISTRIBUTING THE MATERIALS.

8. <u>Limitation of Liability</u>. IN NO EVENT WILL THE CONTRIBUTORS, THE FOUNDATION, ANY MATERIALS LIBRARY, ANY MATERIALS REPOSITORY, OR ANY OTHER PARTY WHO HAS BEEN INVOLVED IN THE DESIGN, CONSTRUCTION, PRODUCTION, DISTRIBUTION, OR ANY OTHER ACTIVITY INVOLVING THE MATERIALS BE LIABLE TO USER OR ANY OTHER PARTY FOR ANY SPECIAL, INDIRECT, INCIDENTAL, RELIANCE, EXEMPLARY, OR CONSEQUENTIAL DAMAGES, INCLUDING LOSS OF DATA OR PROFITS, OR FOR INABILITY TO USE THE MATERIALS, EVEN IF THE CONTRIBUTORS, THE FOUNDATION, OR SUCH OTHER PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES.

9. <u>Interpretation of this User Agreement</u>. This User Agreement shall be interpreted under the laws of the Commonwealth of Massachusetts and the United States of America.

10. <u>Applicability</u>. This User Agreement is binding upon User and its, her, or his heirs, successors, administrators, and assigns.