

# EXTREME GENETIC ENGINEERING

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*An Introduction to Synthetic Biology*

January 2007

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action group on ethics, technology and innovation

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# **EXTREME GENETIC ENGINEERING**

*An Introduction to Synthetic Biology*



**January 2007**

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Original artwork by Reymond Pagé.

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**Extreme Genetic Engineering: An Introduction to Synthetic Biology**  
January 2007

**Nanotech Rx – Medical Applications of Nanoscale Technologies:  
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September 2006

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July/August 2005

**Nanotech's Second Nature Patents: Implications for the Global South**  
June 2005

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November 2004

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*Words that are underlined in this document are defined in the glossary.*

## Extreme Genetic Engineering: An Introduction to Synthetic Biology

**Issue:** Genetic engineering is *passé*. Today, scientists aren't just mapping genomes and manipulating genes, they're building life from scratch – and they're doing it in the absence of societal debate and regulatory oversight. Dubbed “genetic engineering on steroids,” the social, environmental and bio-weapons threats of synthetic biology surpass the possible dangers and abuses of biotech. Synbio is inspired by the convergence of nanoscale biology, computing and engineering. Using a laptop computer, published gene sequence information and mail-order synthetic DNA, just about anyone has the potential to construct genes or entire genomes from scratch (including those of lethal pathogens). Scientists predict that within 2-5 years it will be possible to synthesise any virus; the first *de novo* bacterium will make its debut in 2007; in 5-10 years simple bacterial genomes will be synthesised routinely and it will become no big deal to cobble together a designer genome, insert it into an empty bacterial cell and – voilà – give birth to a living, self-replicating organism. Other synthetic biologists hope to reconfigure the genetic pathways of existing organisms to perform new functions – such as manufacturing high-value drugs or chemicals.

**Impact:** A clutch of entrepreneurial scientists, including the gene maverick J. Craig Venter, is setting up synthetic biology companies backed by government funding and venture capital. They aim to commercialise new biological parts, devices and systems that don't exist in the natural world – some of which are designed for environmental release. Advocates insist that synthetic biology is the key to cheap biofuels, a cure for malaria and climate change remediation – media-friendly goals that aim to mollify public concerns about a dangerous and controversial technology. Ultimately synthetic biology means cheaper and widely accessible tools to build bioweapons, virulent pathogens and artificial organisms that could pose grave threats to people and the planet. The danger is not just bio-terror, but “bio-error.”

Despite calls for open source biology, corporate and academic scientists are winning exclusive monopoly

patents on the products and processes of synthetic genetics. Like biotech, the power to make synthetic life could be concentrated in the hands of major multinational firms. As gene synthesis becomes cheaper and faster, it will become easier to synthesise a microbe than to find it in nature or retrieve it from a gene bank. Biological samples, sequenced and stored in digital form, will move instantaneously across the globe and be resurrected in corporate labs thousands of miles away – a practice that could erode future support for genetic conservation and create new challenges for international negotiations on biodiversity.

**Policy:** In 2006 civil society organizations rejected proposals for self-regulation of synthetic biology put forth by a small group of synthetic biologists. Widespread debate on the social, economic and ethical implications of synbio must come first. Debate must not be limited to biosecurity (bioweapons/bioterrorism) and biosafety (worker safety and environment). The tools for synthesizing genes and genomes are widely accessible and advancing at break-neck pace. It is not adequate to regulate synthetic biology on the national level. Decisions must be considered in a global context, with broad participation from civil society and social movements. In keeping with the Precautionary Principle, ETC Group believes that – at a minimum – there must be an immediate ban on environmental release of *de novo* synthetic organisms until wide societal debate and strong governance are in place.

### **Definition: Synthetic Biology**

(also known as *Synbio*, *Synthetic Genomics*, *Constructive Biology* or *Systems Biology*) – the design and construction of new biological parts, devices and systems that do not exist in the natural world and also the redesign of existing biological systems to perform specific tasks. Advances in nanoscale technologies – manipulation of matter at the level of atoms and molecules – are contributing to advances in synthetic biology.

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## Introduction: Original Syn?

*“Genetic engineering techniques are abysmally primitive, akin to swapping random parts between random cars to produce a better car. Yet our ignorance will fade; biological engineering will become a reality relatively soon.”* – Letter to *New York Times*, 12 December 2000, by Rob Carlson, synthetic biologist and senior scientist in electrical engineering, University of Washington<sup>1</sup>

Transgenics, the kind of engineering you find in genetically modified tomatoes and corn, is old news. As recombinant DNA splicing-techniques turn 30 years old, a new generation of extreme biotech enthusiasts have moved to the next frontier in the manipulation of life: building it from scratch. They call it *synthetic biology*.

Under the old paradigm of transgenics, genetic engineering was a cut and paste affair, in which biotechnologists shuffled pieces of DNA – the self-assembling molecule that instructs living organisms how to carry out every biological process – between already existing species. By contrast, today’s synthetic biologists are armed with the biological equivalent of word processors. They are “beginning the transition from being able to...read genetic code...to the early stages of being able to write code.”<sup>3</sup> Using gene synthesizers, they write the “sentences” of DNA code one “letter” at a time. They can add new letters that have never existed in nature, rearrange them into new “genetic networks” and bundle all that into an artificial “chassis” to go forth and multiply.

Synthetic Biology represents an important change in the direction of genetic technology, which, over much of the past 20 years, has focused on deciphering genetic information (gene sequencing) in

order to identify and understand the role of genes found in nature. As a result of the race to read and map genomes, it is now possible to sequence tens of thousands of base pairs per minute, and to do it relatively cheaply.<sup>4</sup> As attention switches from *reading* to *writing* genetic information (and indeed whole organisms), synthetic biologists can now snub their noses at nature’s designs in favor of made-to-order life-forms. Using engineering concepts borrowed from electronics and computing, synthetic biologists are building simplified versions of bacteria, re-programming DNA as a computing medium and assembling new genetic systems that are human-directed. As they do so, a real world technology with vast applications and implications is fast emerging.

Millions of dollars of government and corporate funding are already flowing into synthetic biology labs. Venture capital and government funding have nurtured the field and the first pure-play synbio companies are now open for business. They hold growing patent portfolios and foresee industrial products for uses as diverse as energy production, climate change remediation, toxic cleanup, textiles and pharmaceutical production. Indeed synthetic biology’s first commercial products may be only a few years from market. Meanwhile the “artificial life

*“...if ever there were a science guaranteed to cause public alarm and outrage, this is it. Compared with conventional biotechnology and genetic engineering, the risks involved in synthetic biology are far scarier.”*

– Philip Ball, consultant editor for *Nature*<sup>2</sup>



*The “artificial life industry” is growing up in a “Wild West” free-for-all environment with virtually no regulatory oversight.*

*Synthetic biologists are making a concerted effort to stave off government scrutiny by making proposals that amount to self-regulation.*

industry” is growing up in a “Wild West” free-for-all environment with virtually no regulatory oversight. In fact, “the synthetic biology community” – as the scientists refer to themselves – is making a concerted effort to stave off government scrutiny by making proposals that amount to self-regulation.

Civil society and social movements, particularly those that have campaigned against genetic engineering and the patenting of life, recognise that “extreme biotech” is a dangerous technology that must not be developed in the absence of widespread societal debate and legally-binding regulation. For some, the quest to build new, living organisms in the laboratory crosses unacceptable ethical boundaries – a reductionist science that raises profound implications for society.

In May 2006, 38 civil society organizations from around the world

joined together in an open letter to the synthetic biology community, expressing concern that “this potentially powerful technology is being developed without proper societal debate concerning socio-economic, security, health, environmental and human rights implications.”<sup>5</sup> As synthetic biology becomes the latest techno-fix for energy, agriculture and medicine in the global South, social movements may soon find that the battle cry of “no to transgenics” needs to be updated: “no to transgenics and synthetics.”

This report outlines the new landscape of synthetic biology by describing its tools, some of the leading protagonists and the various approaches they are pioneering. It will examine some of the emerging applications of synthetic biology and the implications for security, safety, monopoly, justice and livelihoods.

## Box I: BANG Goes Scientific Disciplines: Converging Nanoscale Technologies

Is it biotech? Is it nanotech? Or is it an information technology? The field of synthetic biology is in fact all three – an example of “converging technologies,” the latest industrial strategy favored by OECD policy-makers.

The boundaries between technologies are “really getting sketchy,” says Mark Bunger, a market analyst with Lux Research.<sup>6</sup> Technologists from disciplines such as biotechnology and physics have begun changing places with their colleagues in departments of neurosciences and materials science. All of them manipulate matter on the scale of atoms and molecules (the scale of the nanometer [nm], or one-billionth of a metre): A DNA molecule is 2.5 nm wide and an atom of iron is about .25 nm in diameter. DNA synthesis, for example, involves the manufacture of a biological molecule that encodes information – that’s nanotech, biotech and infotech all in one. DNA computing (described on p. 18) manipulates matter at the nanoscale using the tools of biotechnology to carry out information processing tasks.

Governments and industry around the world enthusiastically embrace (and heavily finance) technological convergence at the nanoscale. The US government, the loudest cheerleader for the convergence strategy, refers to it as NBIC – an acronym derived from the technologies involved: nanotechnology, biotechnology, information technology and cognitive sciences).<sup>7</sup> In Europe, the vision of convergence is called CTEKS (converging technologies for the European knowledge society) and in Canada, convergence is known as BioSystemics Synthesis.<sup>8</sup> Others may refer to acronyms such as GRAIN (Genetics, Robotics, Artificial Intelligence and Nanotechnology),<sup>9</sup> COMBINE (Cogno, Meets Bio, Info, Nanotech)<sup>10</sup> or GRIN (Genetics, Robotics, Informatics and Nanotechnology).<sup>11</sup> Without necessarily sharing the enthusiasm of governments for technological convergence, civil society has come up with its own name: BANG – from *Bits, Atoms, Neurons and Genes*, which are the operable units of the “NBIC” technologies.<sup>12</sup>

**Nanotechnology** – controlling matter through manipulation of **Atoms** –  
can converge with

**Biotechnology** – controlling life through manipulation of **Genes** –  
can converge with

**Information Technology** – controlling data through manipulation of **Bits** –  
can converge with

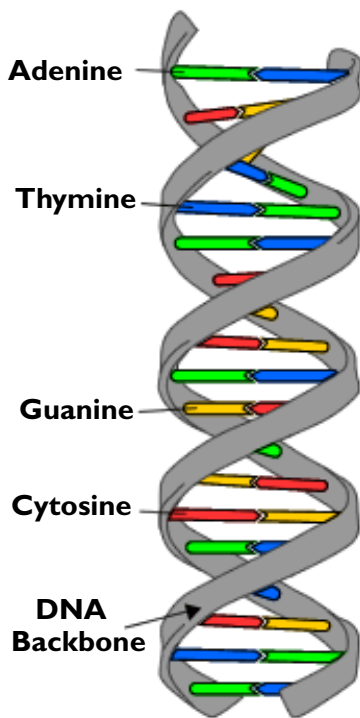
**Cognitive Neuroscience** – controlling minds through manipulation of  
**Neurons**.

Synthetic biology may be the converging technology, *par excellence*. Delve into the biographies of synbio’s luminaries and you’ll find Ph.D.s in chemical, electrical and biochemical engineering, physics and pharmacology (and surprisingly few biologists).

*The boundaries between technologies are “really getting sketchy,” says Mark Bunger, a market analyst with Lux Research.*

*Governments and industry around the world are enthusiastically embracing technological convergence at the nanoscale.*

*Back in 1973 it would take one scientist a whole year to make a length of DNA eleven base pairs long. Today it would take minutes and cost around \$200.*



## Synbio Basics

At the core of synthetic biology is a belief that all the parts of life can be made synthetically (that is, by chemistry), engineered and assembled to produce working organisms. Born in the dot-com communities of Boston and California, much of the vision of synthetic biology is articulated using computing metaphors. DNA code is regarded as the software that instructs life, while the cell membrane and all the biological machinery inside the cell are regarded as the hardware (or wetware as it is sometimes known) that need to be snapped together to make a living organism. This section examines how far synthetic biologists have gone in remaking this soft and wet ware in the lab.

### Read/Write DNA: Gene Synthesis

It's not quite the Biblical feat described in Genesis but if you give Epoch Biolabs of Houston, Texas a thousand dollars they can make a little bit of life (an entire gene) out of chemical dust and post their creation to you within seven days.<sup>13</sup> From Moscow to Montreal, Norway to Nashville a young industry of gene synthesis companies builds artificial life one chemical at a time, ships it as small sections of DNA to labs that are pushing the limits of what is possible in the biotech field. Building artificial DNA is itself nothing new. In the 1960s an Indian-American Nobel prize winner, Har Gobind Khorana, first developed a chemical protocol for building DNA chains to order – arranging its four compounds known as the *nucleotide* bases (adenine, cytosine, guanine,

and thymine represented by the letters A, C, G and T) into the spiraling ladder of the DNA molecule via some fairly slow and complicated chemistry. In 1970 the Nobel laureate and an army of helpers succeeded in constructing the DNA of an entirely artificial gene 207 base pairs long (although it wasn't until 1976 that he and a team of 24 others managed to get their synthetic gene to work). Back in 1973 it would take one scientist a whole year to make a length of DNA eleven base pairs long.<sup>14</sup> Today Khorana's monumental feat would take minutes and would cost around \$200. In the same year that Khorana announced his functional artificial gene (1976), California-based start-up Genentech – the world's first commercial biotech company – invented a faster, automated method of synthesising genes, and so the gene synthesis industry was born.

For the last 30 years the primary use of custom gene synthesis technology has been the production of oligonucleotides (also known as "oligos" or "primers") – short strands of DNA that genetic engineers use as 'hooks' to copy natural DNA in order to decipher the sequence and amplify it. Oligos usually have fewer than 200 bases and are single-stranded (DNA is double-stranded.) Although do-it-yourself desktop DNA synthesisers are used in laboratories to make short stretches of DNA, most grateful biotechnologists send an order over the Internet for the desired DNA sequence to one of the dozens of commercial "Oligo Houses" worldwide. Korea-based

Bioneer Corporation, for example, has the capacity to produce 20,000 oligos per day.<sup>15</sup>

*“We’re going to build you exactly what you are looking for: Whole plasmids, whole genes, gene fragments . . . and in one to two years, possibly a whole genome.”* – John Mulligan CEO of Blue Heron Biotechnology, Washington (USA)<sup>16</sup>

“Gene foundries” – gene synthesis companies that produce longer pieces of double-stranded DNA (including whole genes or genomes) – sell made-to-order sequences over the Internet. ETC has identified at least 66 commercial gene synthesis companies (see world map of gene synthesis companies, p. 8.). The gene synthesis business is growing rapidly and is geographically dispersed. Market estimates are preliminary. According to one industry estimate, the current market (late 2006) for gene synthesis is only \$30-\$40 million per year – a tiny fraction of the \$1-\$2 billion spent on acquiring and modifying DNA.<sup>17</sup> Although the United States is currently home to more gene foundries than any other country, the industry is rapidly moving offshore. Within a few years, notes John Mulligan of Blue Heron Biotechnology, nearly all commercial gene synthesis will be conducted in highly-automated manufacturing facilities.<sup>18</sup> According to Hans Buegl of GeneArt (Regensberg, Germany), the market for gene synthesis has doubled in the past year.<sup>19</sup> Most gene synthesis companies produce lengths of DNA smaller than 3kbp at a time (3000 base pairs – a base pair makes one ‘rung’ of the DNA ‘ladder’), however some companies, such as Blue Heron, can synthesise up to

40kbp (40,000 base pairs) of DNA at one go. Some companies boast that there are no technical limits to the length of DNA they can produce<sup>20</sup> (although most sequences are not error-free). GeneArt claims that it can produce a half-million base pairs of DNA per month<sup>21</sup> – an amount of synthetic DNA that would have kept Khorana busy for over 45,000 years. In July 2006 Codon Devices manufactured and sold a strand of DNA exceeding 35,000 base pairs – what they claim is the largest commercially produced fragment to date.<sup>22</sup> It’s a record that is sure to be broken soon. Synthetic biologists predict that a million base-pair bacterial genome will be constructed within the next two years,<sup>23</sup> that a yeast genome of about 12 million base pairs could be synthesised in about 18-24 months and a plant chromosome would not take much longer. According to engineering professor Drew Endy of Massachusetts Institute of Technology (MIT), “There is no technical barrier to synthesizing plants and animals, it will happen as soon as anyone pays for it.”<sup>22</sup>

In order to build whole genes, companies employ dedicated DNA synthesis machines – using either their own proprietary technology (such as Blue Heron’s GeneMaker technology<sup>25</sup>) or commercially available gene-synthesis equipment (from a manufacturer such as ABI<sup>26</sup>). While a good DNA synthesiser can now be purchased for less than \$10,000, older synthesisers can be bought secondhand for under \$1000. Professor Endy speculates that do-it-yourself synthesisers could be built using parts found in a hardware store.<sup>27</sup> The DNA itself is constructed from

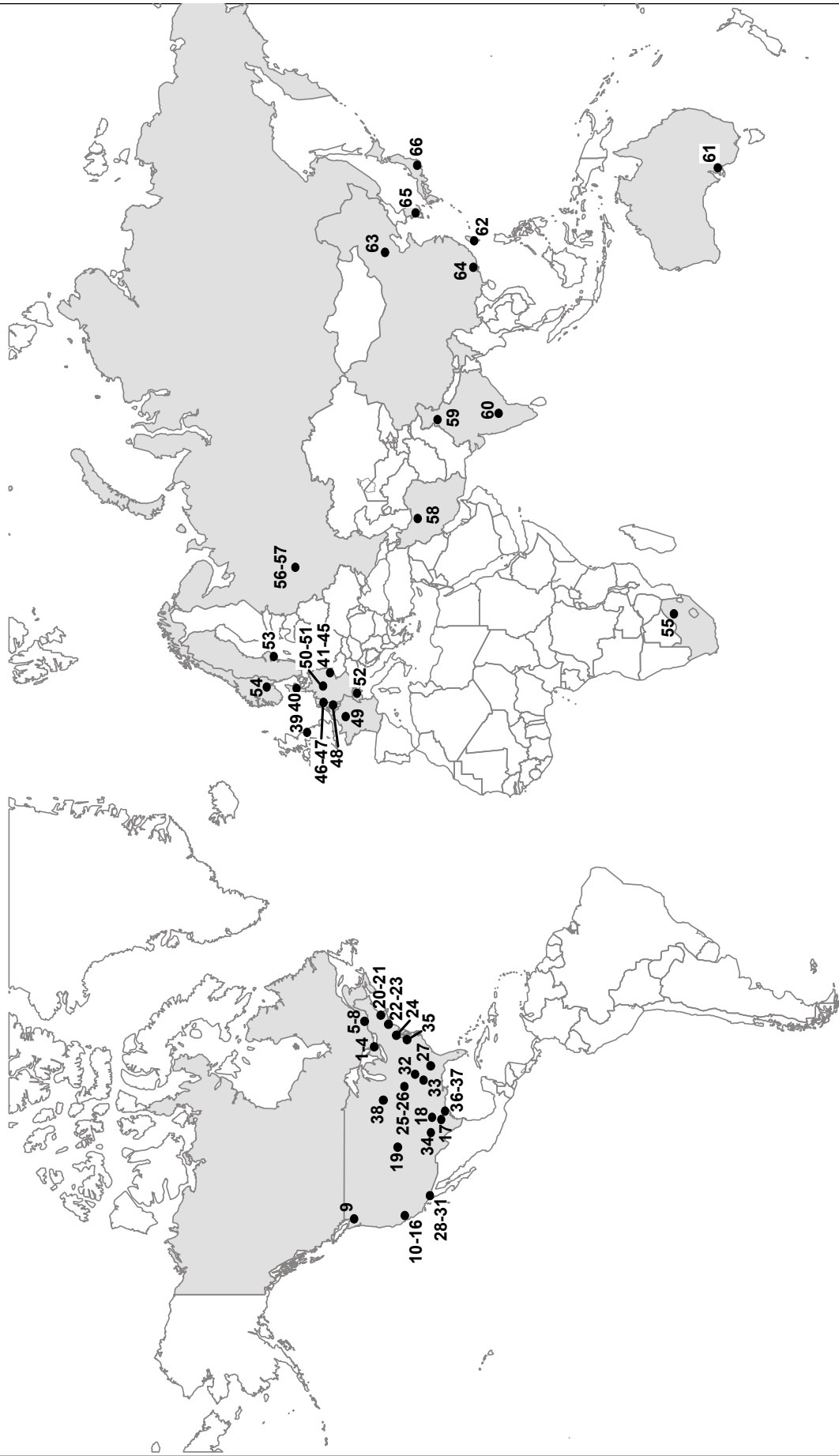
*“There is no technical barrier to synthesizing plants and animals, it will happen as soon as anyone pays for it.”*

— Drew Endy, MIT

*“Within a decade a single person could sequence . . . his or her own DNA within seconds.”*

— Rob Carlson,  
University of Washington

# Map: Commercial DNA Synthesis Companies



cheaply-produced sugar isolated from sugar cane. According to synthetic biologist Rob Carlson at University of Washington (USA), efficiency improvements in gene synthesis machines are now speeding up as fast, if not faster, than Moore's Law (the famous prediction by Gordon Moore, founder of Intel, that

computer processors would double their speed and half their size every two years).<sup>28</sup> According to Carlson, "Within a decade a single person could sequence or synthesise all the DNA describing all the people on the planet many times over in an eight-hour day or sequence his or her own DNA within seconds."<sup>29</sup>

*Efficiency improvements in gene synthesis machines are now speeding up as fast, if not faster, than Moore's Law.*

## Key to Map

1. Cortec DNA Service Laboratories, Inc. - Kingston, ON, Canada
2. Fermentas International Inc. - Burlington, ON, Canada
3. Norclone - London, ON, Canada
4. Biobasic - Markham, ON, Canada
5. Alpha DNA - Montreal, QC, Canada
6. BioCorp - Montreal, QC, Canada
7. Bio S&T - Montreal, QC, Canada
8. Top Gene Technologies - Montreal, QC, Canada
9. Blue Heron Biotechnology - Bothell, WA, USA
10. DNA2.0 - Menlo Park, CA, USA
11. mclab - San Francisco, CA, USA
12. Genemed Synthesis - San Francisco, CA, USA
13. FastaDNA - San Francisco, CA, USA
14. BioNexus /ABP - Oakland, CA, USA
15. Invitrogen - Carlsbad, CA, USA
16. Biosearch Technologies Inc. - Novato, CA, USA
17. Ambion Inc. - Austin, TX, USA
18. Bio-Synthesis Inc. - Lewisville, TX, USA
19. Dharmacon Inc. - Lafayette, CO, USA
20. ChemGenes Corporation - Wilmington, MA, USA
21. Codon Devices - Cambridge, MA, USA
22. Gene Link Inc. - Hawthorne NY, USA
23. GenScript - Piscataway, NJ, USA
24. BioServe Biotechnologies Ltd - Laurel, MD, USA
25. Sigma Aldrich-Genosys - St. Louis, MO, USA
26. IBA - St. Louis, MO, USA
27. AnaGen Technologies - Atlanta, GA, USA
28. Bio Applied Technologies Joint - San Diego, CA, USA
29. Retrogen - San Diego, CA, USA
30. Eton Bioscience - San Diego, CA, USA
31. Illumina Inc. - San Diego, CA, USA
32. Celtek - Nashville, TN, USA
33. Operon Biotechnologies - Huntsville, AL, USA
34. Certigen - Lubbock, TX, USA
35. Commonwealth Biotechnologies - Richmond, VA, USA
36. Epoch Biolabs - Houston, TX, USA
37. Picoscript - Houston, TX, USA
38. Integrated DNA Technologies - Coralville, IA, USA
39. Yorkshire Bioscience Ltd. - York, UK
40. DNA Technology A/S - Aarhus, Denmark
41. Geneart - Regensburg, Germany
42. Entelechon - Regensburg, Germany
43. MWG-Biotech AG - Ebersberg, Germany
44. Eurofins Medigenomix - Martinsried, Germany
45. Metabion International AG - Munich, Germany
46. Biolegio bv - Nijmegen, The Netherlands
47. BaseClear - Leiden, The Netherlands
48. Eurogentec s.a. - Seraing, Belgium
49. Genosphere Biotechnologies - Paris, France
50. BioSpring - Frankfurt, Germany
51. IBA - Gottingen, Germany
52. Microsynth - Balgach, Switzerland
53. CyberGene AB - Huddinge, Sweden
54. Medprobe - Oslo, Norway
55. Inqaba Biotechnical Industries Ltd - Pretoria, South Africa
56. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences - Moscow, Russia
57. Evrogen - Moscow, Russia
58. CinnaGen Inc. - Tehran, Iran
59. Imperial Bio-Medic (P) Ltd. - Chandigarh, India
60. BioServe Biotechnologies Pvt Ltd. - Hyderabad, AP, India
61. GeneWorks Pty Ltd. - Thebarton SA, Australia
62. ScinoPharm Taiwan Ltd. - Shan-Hua, Taiwan
63. Takara Biotechnology (Dalian) Co., Ltd. - Dalian, China
64. Tech Dragon - Hong Kong, China
65. Bioneer Corporation - Daedeok-gu, Korea
66. jBioS, Japan Bio Services Co. Ltd. - Asaka City, Japan

**“DNA is getting pretty  
freaking cheap to make.”**

— Andrew Hessel, bioinformaticist

**DNA synthesis reduces the  
time it takes genetic engineers  
to isolate and transfer DNA  
in order to build genetically  
modified organisms.**

## **Box 2: Life is cheap – and fast.**

*“In 2000, the cost of assembling sequences to order was roughly \$10 to \$12 per base pair... Some scientists foresee DNA synthesis dropping to 1 cent per base pair within a couple of years. That’s a gene for 10 bucks, a bacterial genome for the price of a car.” – Oliver Morton, “Life Reinvented,” *Wired*<sup>30</sup>*

Back in the summer of 2000, John Mulligan, CEO of gene synthesis company Blue Heron Biotechnology, boasted that the price of gene synthesis was dropping so quickly that, “If you look at the curve, it’s headed to about zero in 2006.”<sup>31</sup> Blue Heron isn’t giving away synthetic DNA yet, but their product has dramatically dropped in price, or, as Andrew Hessel, a bioinformaticist in Toronto puts it: “DNA is getting pretty freaking cheap to make.”<sup>32</sup> In mid-2006 ETC Group surveyed advertised costs and found that most gene synthesis companies currently charge between US\$1-\$2 dollars per base pair (around “a buck a base” as they like to say).<sup>33</sup> The cheapest advertised rate was Epoch Biolabs, at \$.85 per base pair.<sup>34</sup> In October 2006, Codon Devices advertised \$.79 per base pair.<sup>35</sup> At a May 2006 synthetic biology conference gene synthesis companies were confidently predicting that the price would drop to \$.50 per base pair by the end of 2007.<sup>36</sup> Gene synthesis for oligos (shorter, single strands) is already at \$.10 per base and a new method pioneered by geneticist George Church of Harvard University may reduce the cost ten-fold, to \$.01 per base.<sup>37</sup>

Our informal survey suggests that most of the synthesis companies can turn around a synthetic gene (around 1,000 base pairs known as 1 kilo-base pair – Kbp) in under two weeks. At present Craig Venter holds the world’s gene-speed record for synthetically producing a 5,386 bp genome (of the virus phiX 174) in under 14 days (although there were errors in his copy).<sup>38</sup> If you want to order that same synthetic virus from Epoch Biolabs they would charge you less than \$6000 to synthesise the organism, but it might take a few weeks longer. Ordering something more complex, such as a synthetic copy of the smallest bacterial genome, *Carsonella rudii* (159,622 base pairs) would likely set you back about \$126,000 at today’s rates. Today’s DNA synthesis techniques allow us to put a theoretical price on human life: building the entire genome of a human being – around 3 billion base pairs – could be done today by a bargain basement synthesis company for just over \$2.5 billion dollars – well within the reach of several individuals on the planet. Drew Endy of MIT speculates that within 20 years human genomes will be synthesised from scratch.<sup>39</sup>

Meanwhile, the growth of the DNA synthesis industry is making existing technologies quicker, cheaper and easier. DNA synthesis reduces the amount of time it takes genetic engineers to isolate and transfer DNA in order to build genetically modified organisms – tedious activities that consume as much as 50% of GMO research.<sup>40</sup> With DNA synthesis technology, lab scientists can now order the complete genes they require in a matter of weeks, a huge short-cut in production.

## **Cleaning Up the Code – Codons, Proteins and Pathways**

Cranking out DNA is pointless unless scientists know how to arrange it into meaningful code. In the popular understanding of genetics, a gene, a length of DNA composed of base pairs, is regarded as the smallest functional unit of genetic code, instructing cellular machinery via RNA (ribonucleic acid) which proteins to manufacture. Those proteins in turn carry out the tasks and processes within organisms that we understand to be “life.” As Francis Crick, a co-discoverer of the DNA double-helix, put it: “DNA makes RNA, RNA makes proteins, and proteins make us.”<sup>41</sup> The building blocks of those all-important proteins are amino acids – 20 unique amino acids have been identified – and it is the codon that determines which amino acid will be produced within the cell. Codons are trinucleotides – that is, a series of three (out of four) chemical bases – linked together in a specific order. It is that order that determines which amino acid will be added to the protein under construction. Each codon carries the code for a specific amino acid.

Synthetic biologists want to work below the level of the gene, at the level of the codon – to identify codons and rearrange them to build new sets of biological instructions. Because there are 64 possible codons (four bases linked together in sets of three, or  $4^3$ ) but only 20 different amino acids they translate into, synthetic biologists can choose among different options for codons when they want to express a specific amino acid (known as codon optimization). It may be that one codon

works better in bacteria and another in plants even though both produce the same amino acid.<sup>42</sup>

Some synthetic biologists take the approach of combing through the genetic code of existing organisms and removing or reducing unnecessary codons to get a sleeker version of the genetic code. Others, by combining codons into stand-alone programming instructions, are developing “standard parts” analogous to the standard parts of electronic circuitry or the standard commands of a computer language. They keep an inventory of these standard parts, and are making them available for others to assemble into more complex genetic systems. Others are designing entirely new artificial amino acids that result from codon combinations not found in nature. In the US and Europe some synthetic biologists hope to build an artificial “protocell” that will contain and express synthetic DNA as flexibly as a computer stores document files and runs computer programmes.

Unfortunately for would be life-builders, genetic code is not as linear as computer code. While the popular view of genetics links units of DNA (genes) to specific traits, the reality is messier. In real life, genes and parts of genes co-operate in subtle and complex networks, each producing proteins that promote or suppress the behaviour of other genes. The result is a system of cellular regulation that controls the amount or timing by which a substance or trait is produced – a bit like electronic circuits that regulate electrical current. Geneticists interested in manipulating genomes have begun mapping the interactions between genes to try

*Cranking out DNA is pointless unless scientists know how to arrange it into meaningful code.*



*Unfortunately for would be life-builders, genetic code is not as linear as computer code.*

to determine the full set of interactions necessary to produce a desired protein. They can represent these networks with circuit diagrams similar to those used in electronics. The set of interactions that involve a network of DNA molecules acting together to produce a protein can be referred to as a “genetic pathway” and synthetic biologists are now trying to rebuild or alter these genetic pathways as discreet sections of the

genome. This involves designing not just one coding region of DNA, but several different areas of code, and then putting them together as a synthetic chromosome. By altering these networks and pathways, synthetic biologists can increase the production of a protein or stimulate the production of an entirely different substance, such as a plastic or a drug.<sup>43</sup>

## Five Alive – An Introduction to Five Major Areas of Research in Synthetic Biology

*“We want to demonstrate what the heck life is by constructing it. If we do that, we’re going to have a very big party. The first team that does it is going to get the Nobel Prize.”*<sup>44</sup> – Steen Rasmussen, Synthetic Biologist at Los Alamos National Laboratory in New Mexico

The world’s first synthetic biology conference convened in June 2004. Two months later, the University of California at Berkeley announced the establishment of the world’s first synthetic biology department. In 2005, three synthetic biology start-ups attracted over \$43 million in venture capital, and in late 2006 there’s talk of establishing an industry trade group for gene synthesisers. The nascent field of synthetic biology is closely identified with a handful of high-profile scientists (mostly men) who articulate grand visions, and are striking different paths toward the common goal of creating artificial life. Some researchers are trying to build synthetic biology’s basic enabling technologies. Others are focusing on real-world applications. In the following pages, ETC Group profiles some of synthetic biology’s leading practitioners and reviews five major areas that are being developed to build and use artificial life. These include:

- 1. Making Minimal Microbes – Post-modern Genomics**
- 2. Assembly-Line DNA – “Lego” Life-forms to Order**
- 3. Building Artificial Cells from the Bottom Up – Ersatz Evolution**
- 4. Pathway Engineering – Bug Sweatshops**
- 5. Expanding Earth’s Genetic System – Alien Genetics**

### **I: Making Minimal Microbes – Post-modern Genomics**

In the race to synthesise life, genomics mogul J. Craig Venter often overshadows the rest of the pack. Venter, dubbed “Biology’s Bad Boy,” led the private company Celera, which, in the 1990s, sold human genome data to pharmaceutical companies faster than the National Institutes of Health – Celera’s competitor in the race to map the human genome – were able to decode it.<sup>45</sup> In 1995 Venter announced that he was first to sequence the entire genome of a living organism (the bacterium known as *Hemophilus influenzae*).<sup>46</sup> In 2003 Venter made headlines when his team created the first synthetic virus from scratch – and it took them only 14 days to do it. Venter is notorious for pushing the boundaries on the commercial exploitation of life. His newest commercial venture, Synthetic Genomics, Inc., founded in 2005 with \$30 million in venture capital, aims to commercialise a range of synthetic biology applications, starting with energy production.<sup>47</sup>

In the mid 1990s Venter’s non-profit outfit, The Institute for Genomic Research (TIGR), pursued a Minimal Genome Project to discover the fewest number of genes necessary for a bacterium to survive. The bacterium they chose was *Mycoplasma genitalium*, a bug that causes urinary

*“We want to demonstrate what the heck life is by constructing it.”*

— Steen Rasmussen, Synthetic Biologist, Los Alamos National Laboratory (USA)

*Venter is notorious for pushing the boundaries on the commercial exploitation of life. His newest commercial venture is Synthetic Genomics, Inc.*

*Exotic microbes are the raw materials for creating new life-forms and new energy sources.*

*Venter claims his will be the first fully synthetic life-form, but the birthdate of his new organism is shrouded in secrecy.*

tract infections. It has one of the smallest known genomes of any living organism (517 genes made up of about 580,000 DNA base pairs). Clyde Hutchison of TIGR began modifying the genome of *Mycoplasma genitalium*, observing which genes could be disrupted without killing the organism and then disabling those genes one at a time. He guessed that the bacterium might be able to survive with almost half its genes removed.<sup>48</sup> In a 2005 workshop at the US Department of Energy, Hutchison's team announced that they had reduced the genome to about 386 essential genes. In another bacterium, *Bacillus subtilis*, they found that all but 271 of 4100 genes could be knocked out.<sup>49</sup> Others are now trying to minimise the genome of organisms such as *E. coli*.<sup>50</sup>

For Venter's team, the ultimate goal of creating a minimal microbe is to use it as a platform for building new, synthetic organisms whose genetic pathways are programmed to perform commercially useful tasks – such as generating alternative fuels. Hutchison, Venter and Nobel laureate Hamilton Smith are now attempting to artificially synthesise their reduced version of the *Mycoplasma genitalium* genome so it could be used as a stripped-down 'chassis' for future synthetic organisms. They will remove the DNA from an existing bacterium and insert their synthesised genome in its place.<sup>51</sup> If it successfully 'boots up,' their synthetic organism, dubbed *Mycoplasma laboratorium*, would amount to an entirely new species of bacterium – the first fully synthetic living species ever created (viruses must use a host cell's machinery in order to replicate and are therefore not

considered living organisms). Venter calls *Mycoplasma laboratorium* a "synthetic chromosome" and his intention is to use it as a flexible bio-factory into which custom-designed synthetic "gene-cassettes" of four to seven genes can be inserted, genetically programming the organism to carry out specific functions.<sup>52</sup> As a first application, Venter hopes to develop a microbe that would help in the production of either ethanol or hydrogen for fuel production (see The New Synthetic Energy Agenda p. 27). He is also looking to harness the mechanisms of photosynthesis to more effectively sequester carbon dioxide, ostensibly as a means of slowing climate change.

Venter's team should have plenty of genetic booty to exploit following its US government-funded ocean expedition on Venter's yacht to collect and sequence microbial genetic diversity from around the globe. Exotic microbes are the raw materials for creating new life-forms and new energy sources. Venter claims that his expedition has discovered 3,995 new gene families not previously known, and 6-10 million new genes – which he describes as "design components of the future."<sup>53</sup> To harness synthetic microbes for energy production, Venter's non-profit institutes have received over \$12 million from the US Department of Energy's Genomes to Life project.<sup>54</sup> In February 2006 the former head of that government programme, Aristides Patrinos, became the president of Venter's Synthetic Genomics.<sup>55</sup>

Venter talks big. In 2004 he predicted that "engineered cells and life-forms [will be] relatively common within a decade." And he claims his will be the first fully synthetic life-

form.<sup>56</sup> The birthdate of Venter's new organism is shrouded in secrecy. In August 2004 Venter boasted to *Wired* magazine that there would be an announcement by the end of the year.<sup>57</sup> It never came. In June 2005 Venter told the *Wall Street Journal* that he was two years away from completing the synthetic microbe and that the number of people working on the project was about to jump from 30 to 100.<sup>58</sup> In February 2006 Venter told a Hollywood gathering that his team was just a few months away from creating an artificial organism and, once that happened, the biotech field would be blown wide open.<sup>59</sup> Venter took a more somber tone at this year's synthetic biology conference in Berkeley (SynBio 2.0), predicting that his organism would be ready within two years, admitting that it has been "a rolling two years" for some time now.<sup>60</sup>

Venter's attempt to build an artificial chromosome is among synbio's most high-profile projects. It also has the most visible commercial backing, including corporate agriculture and energy interests. Synthetic Genomics received half its start-up capital from Alfonso Romo Garza, the Mexican billionaire who owns agribusiness giant Savia.<sup>61</sup> Bloggers at the University of California-Berkeley conference known as SynBio 2.0 noted that Venter was conspicuously conversing with Silicon Valley's top venture capital investor, Vinod Khosla – the co-founder of Sun Microsystems and a big proponent of ethanol-based fuels.<sup>62</sup> Accustomed to pushing ethical envelopes, Venter expects his artificial life-form to raise eyebrows, and his institute is one of three heading

a study on the ethics of synthetic biology, which will no doubt serve as a pre-emptive strike against critics.<sup>63</sup> When asked by interviewers if they are playing God, Venter's colleague Hamilton Smith gives a characteristically hubristic response: "We don't play."<sup>64</sup>

## **2: Assembly Line DNA – "Lego" Life-forms to Order**

Craig Venter and Hamilton Smith may not want to play, but Drew Endy certainly does. Endy is a thirty-something MIT professor who helped coin the term *synthetic biology*.<sup>65</sup> "I like to build stuff," he told *Wired*. "I'm a kid in that regard."<sup>66</sup> He and his grad school followers project themselves as the hip, young antithesis to Venter's grown-up corporate biology. Instinctively populist, they publish comics about synthetic biology, edit light-hearted videos about life in the lab and carry out their discussions over Internet blogs and wikis (editable webpages). Endy, an engineer by training, is also a computer programmer and he and those around him use computer and electronics metaphors to describe synthetic biology: A living organism is a 'computer' or 'machine' made up of genetic 'circuits' in which DNA is the 'software' that can be 'hacked.' He points out that, "Biological engineers of the future will start with their laptops, not in the laboratory."<sup>67</sup> Endy's engineering approach dismisses genetic code that evolved in nature because it's too messy and too redundant. He would rather invent his own code. "I thought, Screw it," Endy told *Wired*. "Let's build new biological systems – systems that are easier to understand because we made them that way."<sup>68</sup>

**"We don't play."**

— Hamilton Smith, responding to an interviewer asking if he and colleagues are playing God

**"Biological engineers of the future will start with their laptops, not in the laboratory."**

— Drew Endy, MIT

*Last year, almost forty teams of synthetic biology students from around the world competed to create the “coolest” artificial life-form.*

*“If you can take even the most rudimentary concepts of electrical engineering and can pull them off in a cell, the control that could give you and the applications are mind-boggling.”*

Emanuel Nazareth, quoted in *The Globe and Mail*

Endy longs for a logical and predictable biotechnology, what he and others refer to as “intentional biology.” “We would like to be able to routinely assemble systems from pieces that are well described and well behaved,” Endy explains. “That way, if in the future someone asks me to make an organism that, say, counts to 3,000 and then turns left, I can grab the parts I need off the shelf, hook them together and predict how they will perform.”<sup>69</sup>

To do this he and his colleague at MIT, artificial intelligence pioneer Tom Knight, have invented several hundred discrete DNA modules that behave a little like electronic components. They include sequences that turn genes off and on, transmit signals between cells or change colours between red, green, yellow and blue. Knight and Endy then encourage others to combine those modules into more complex genetic circuits. They call these modules Biobricks or “standard parts” and their non-profit BioBricks Foundation maintains over 1500 BioBricks in its registry of standard parts that can be freely used by other synthetic biology researchers.<sup>70</sup> Each of these BioBricks is a strand of DNA designed to reliably perform one function and to be easily compatible with other BioBricks in making longer circuits. The completed circuits are then dropped into *E. coli*, yeast or another microbial host to see if they function. The inspiration for BioBricks are the brightly coloured plastic bricks from the children’s toy known as Legos, of which Tom Knight is a lifelong fan.<sup>71</sup>

Every year Endy, Knight and their fellow synthetic biologists at MIT

convene an International Genetically Engineered Machine Competition (known as iGEM). Last year, almost forty teams of synthetic biology students from around the world competed to create the “coolest” artificial life-form out of BioBricks.<sup>72</sup> According to the event’s organisers, “Jaw-dropping creativity, originality, and functionality will certainly be factors in the Judge’s [sic] decisions of relative coolness.”<sup>73</sup>

In line with the criterion of cool, iGEM, now in its fifth year, mostly produces eye-catching gimmicks – bacteria that blink different colours and biological films that can be programmed to take simple photographs and display images. In 2006 the iGEM team from MIT designed *E. coli* bacteria that smell of bananas and wintergreen.<sup>74</sup> Behind these trivial applications are ones that could someday prove practical (and lucrative). Biological films that take photographs could be the basis of new forms of lithography for assembling computer circuits, while sweet smelling bacteria could interest the fragrance and flavouring industries. Endy talks about building circuits into human body cells that count how many times they divide in order to prevent run-away cell growth. “I could hook it up to a suicide mechanism,” he speculates, “and any cell that divides more than 200 times, it would say, ‘Kill it, it’s forming a tumour’...”<sup>75</sup> One of Endy’s long term ambitions is to re-design the seeds of a tree such that the tree is programmed to grow into a house.<sup>76</sup> One iGEM participant, Emanuel Nazareth of the University of Toronto, imagines using BioBricks to build programmable cells that scour

the body crunching through cholesterol: “If you can take even the most rudimentary concepts of electrical engineering and can pull them off in a cell,” Nazareth explains, “the control that could give you and the applications are mind-boggling.”<sup>77</sup>

Mind-boggling applications that are already attracting big money: iGEM organiser Randy Rettberg reminds competitors, “The goal is not just to do science and something cool. It is to make an industry.”<sup>78</sup> The US-based synthetic biology community, centred close to the dot.com hot-spots of Silicon Valley and Boston, attracts young graduates planning synthetic biology start-ups in the hope of becoming the next Google or Yahoo. They call this “garage bio-hacking,” consciously emulating the small, informal and homegrown software companies of Silicon Valley. At a recent gathering of synthetic biologists, bloggers commented how the field “has an interesting new flavor, namely that of money,” with venture capitalists and established companies sniffing around for investment prizes.<sup>79</sup> In 2005, Endy and Knight, along with several other synthetic biology illuminati, raised \$13 million to found their own synthetic biology start-up. Known as Codon Devices, the company is described as a ‘biofab.’ The aim of Codon Devices is to “eliminate construction as a barrier to synthetic biology.”<sup>80</sup> This means that Codon Devices builds DNA to order, inserts it in bacteria and sends it back to the customer as a living cell culture – providing a shortcut for genetic engineers.

### **3: Building Artificial Cells from the Bottom Up – Ersatz Evolution**

#### **From A-Bomb to A-Life: The Latest Project in New Mexico’s Desert:**

One synbio research team is attempting to create artificial life-forms without using DNA at all. In October 2004, theoretical physicist Steen Rasmussen won a \$5 million grant from Los Alamos National Laboratory (New Mexico, USA) – the atomic bomb’s birthplace – to build a living cell entirely from scratch. While most synbio projects are top-down – re-arranging existing life or reverse-engineering it to arrive at life’s barest essentials – Rasmussen’s project is truly bottom-up: He is trying to design life by creating its essential ingredients and mixing them together in a test tube.<sup>88</sup> His research team believes their “protocell” will require three elements to sustain life – a metabolism that harvests and generates energy, an information-storing molecule (like DNA) and a membrane to hold it all together.<sup>89</sup>

Rasmussen is tweaking nature’s cell design for his “Los Alamos Bug.” Rather than an oily membrane keeping water inside, his cell is basically a droplet of oil, which keeps water on the outside.<sup>90</sup> Furthermore, it uses a different double helix molecule to carry instructions: Rather than DNA, the Los Alamos Bug uses human-made PNA – peptide nucleic acid. PNA has the same structure and is made from the same chemical bases as DNA – G, C, A and T – but the molecule’s backbone is made of peptides, the build-

*One synbio research team is attempting to create artificial life-forms without using DNA at all.*

*Steen Rasmussen’s research team is trying to design life by creating its essential ingredients and mixing them together in a test tube.*

*It would take more than a trillion music CDs to hold the amount of information that DNA can hold in a cubic centimeter.*

### **Box 3: DNA Computing: Nature's PowerBook**

While Endy and his cadre use computer code to build life, others are using life to build computers. The fledgling science of DNA computing is founded on the insight that, like a computer, DNA both stores and processes coded information. DNA computing was born in 1994 when Leonard Adleman, professor of computer science at the University of Southern California, demonstrated how to solve a complex computational problem (whose solution he already knew) using DNA to sort through possible answers and find the correct one.

While computers store and process information in binary strings – coded as the numbers 0 and 1 – DNA operates in (mathematical) base four. Its information is coded by the sequence of the four nucleotide bases, A, C, T and G. The bases are spaced every 0.35 nm along the DNA molecule, giving DNA a data density of over one-half million gigabits per square centimeter, many thousands of times more dense than a typical hard drive.<sup>81</sup> For example, it would take more than a trillion music CDs to hold the amount of information that DNA can hold in a cubic centimeter.<sup>82</sup> Moreover, different strands of DNA can all be working on computational problems at the same time – and are a lot cheaper than buying multiple PowerBooks. Adleman's rudimentary DNA computer performed 10<sup>14</sup> operations per second.<sup>83</sup>

DNA computers are still in the proof-of-principle stage – they look nothing like computers – just DNA strands suspended in liquid, and practical applications are in very early stages. But it is the potential to exploit DNA's storage and processing capacity that excites researchers. In 2000, Adleman asked, "...if you can build a computer, then what other useful devices could you build on that very small scale? The possibilities are endless."<sup>84</sup>

One hope is that DNA computers can function as sensors. With funding from the US National Aeronautics and Space Agency (NASA), Columbia University researcher Milan Strojjanovic is developing a DNA computer that will act as a biosensor to monitor the health of astronauts.<sup>85</sup> Meanwhile, scientists at Israel's Weizmann Institute, led by Ehud Shapiro, are developing a DNA computer to recognise and treat disease. In an *in vitro* experiment, a DNA computer was able to detect abnormal activity in four targeted genes that are associated with prostate and lung cancer. Not only that, after recognizing the malignancy, the computer released a drug suppressing the genes responsible for the abnormal activity.<sup>86</sup> The researchers hope to develop an injectable version that could work inside the body – an accomplishment that could take decades.

Ned Seeman, working with DNA computers at New York University, is trying to apply DNA's self-assembly process to the manufacture of nanoscale structures. While hoping to make the most of DNA's computing potential, he remains cautious: "DNA computation is sort of like aviation in about 1905. There was such a thing as an airplane, but who knew if it was actually going to become a major mode of transportation or just sort of a toy?"<sup>87</sup>

ing blocks of proteins – instead of DNA’s sugar-phosphate backbone. Howard Packer, Rasmussen’s collaborator as well as a pioneer of chaos theory, says that using PNA rather than DNA is a good idea for biosafety reasons. Because PNA doesn’t exist in nature, he says, the Bug may be easier to control so it doesn’t “escape and cause problems.”<sup>91</sup>

Rasmussen and Packard have established a synthetic biology start-up based in Venice, Italy, ProtoLife, to commercialise the Bug and/or its components. While Packard acknowledges that their bottom-up approach appears to lag behind life-creating teams led by Venter, Endy and Jay Keasling (see below), he argues that the protocell approach will lead to a better understanding of living and non-living systems. “Right now,” he contends, “the state of the art for synthetic biology is a hodgepodge of techniques which is, from an engineering and scientific perspective, groping.”<sup>92</sup> Rasmussen said, in February 2005, that he couldn’t promise a functioning cell in three years – about the time it took to build the atomic bomb – but he “can guarantee that we’ll have good progress.”<sup>93</sup>

There’s a good chance that the first lab to produce a working, evolving protocell will be, like ProtoLife, a member of the PACE consortium. PACE – Programmable Artificial Cell Evolution – is a project involving 14 European and US universities and companies and is funded by the European Commission. PACE has received over €6.5 million through the Commission’s 6<sup>th</sup> Framework Programme.<sup>94</sup>

#### 4: Pathway Engineering – Bug Sweatshops

*“Really, we are designing the cell to be a chemical factory. We’re building the modern chemical factories of the future.”*

– Jay Keasling, Professor of Chemical Engineering, University of California at Berkeley<sup>95</sup>

At the University of California at Berkeley, the synthetic biology department led by Jay Keasling is engineering the genetic pathways of cells to produce valuable drugs and industrial chemicals – a goal that is fast becoming the *cause célèbre* of synbio. “Chemical engineers are good at integrating lots of pieces together to make a large scale chemical plant, and that is what we’re doing in modern biological engineering – we’re taking lots of little genetic pieces and putting them together to make a whole system,” explains Keasling.<sup>96</sup>

Keasling’s team has synthesised about a dozen genes that work together to make the chemical processes (or ‘pathways’) behind a class of compounds known as isoprenoids – high-value compounds important in drugs and industrial chemicals. Isoprenoids are natural substances produced primarily by plants. Because of their structural complexity, chemical synthesis of most isoprenoids has not been commercially feasible, and isolation from natural sources yields only very small quantities. Synthetic biologists at Berkeley hope to overcome these limitations by designing new metabolic pathways in microbes, turning them into “living chemical factories” that produce novel or rare isoprenoids.<sup>97</sup> Most notably, they are focusing on a powerful anti-malarial compound

*“We’re building the modern chemical factories of the future.”*

— Professor Jay Keasling, University of California, Berkeley



*Backed by a \$42.5 million grant from the Bill and Melinda Gates Foundation, the Berkeley team believes that synthetic biology is the tool that will allow unlimited and cheap production of a previously scarce drug to treat malaria in the developing world.*

*Amyris “is now poised to commercialize pharmaceuticals and other high value, fine chemicals taken from the world’s forests and oceans by making these compounds in synthetic microbes.”*

—Amyris Biotechnologies website

known as artemisinin. Backed by a \$42.5 million grant from the Bill and Melinda Gates Foundation, the Berkeley team believes that synthetic biology is the tool that will allow unlimited and cheap production of a previously scarce drug to treat malaria in the developing world. In 2003 Keasling and colleagues founded a synbio start-up called Amyris Biotechnologies to bring the project to fruition. (See Case Study, p. 52.)

Amyris hopes to use the same technology platform to produce far more lucrative drugs. “A number of drugs can be produced this way, not just one,” Keasling explains.<sup>98</sup> “We’ve essentially created a platform that will allow you to produce many drugs cheaper. Down the road, we will be able to modify enzymes to produce a number of different molecules, even some that don’t exist in nature.”<sup>99</sup>

According to the company’s website, Amyris “is now poised to commercialize pharmaceuticals and other high value, fine chemicals taken from the world’s forests and oceans by making these compounds in synthetic microbes.”<sup>100</sup> There are thousands of isoprenoid compounds and many of them have industrial uses. Amyris plans to use synthetic biology to produce commercial drugs, plastics, colourants, fragrances and biofuels. The company claims that its microbially-derived chemicals could be used for remediation of radioactive materials and to neutralise dangerous toxins such as sarin. Keasling’s lab is also attempting to re-engineer the metabolic pathways

that produce natural rubber (also an isoprenoid).<sup>101</sup> These pathways will then be incorporated into bacteria, or in sunflowers or desert plants, to boost rubber production (see Synthetic Commodities, p. 40).

Other researchers exploring commercial uses for pathway engineering, include:

Chris Voigt, a synthetic biologist at the University of California at San Francisco announced in May 2006 that he had re-engineered a strain of salmonella to produce the precursor to spider silk – a substance as strong as Kevlar with 10 times the elasticity.<sup>102</sup>

California-based Genencor has been working with chemical giant DuPont to add synthetic genetic networks to the cellular machinery of *E. coli*. When mixed with corn syrup in fermentation tanks, their modified bacterium produces a key component in Sorona, a spandex-like fibre. DuPont and sugar giant Tate & Lyle are building a \$100-million biological factory in Tennessee, which they plan to complete in late 2006, to produce this new biomaterial.<sup>103</sup> DuPont hopes that its new bio-based textile will cause as much fuss as the introduction of nylon back in the 1930s. DuPont plans to build additional Sorona production factories, probably in the global South. According to John Ranieri, Dupont’s vice-president of bio-based materials, “one thing is for sure: we need to be close to the agricultural producing centers, in Brasil, India or the USA.”<sup>104</sup>

## 5: Expanding Earth's Genetic System – Alien Genetics

*“We’re not trying to imitate nature; we’re trying to supplement nature. We’re trying to expand the genetic code.”* – Dr. Floyd E. Romesburg, Scripps Research Institute, *New York Times*, July 24, 2001

While astronomers look to the stars for signs of alien life, a group of synthetic biologists are creating it in a Petri dish. Steven Benner, a biochemist and founder of the Westheimer Institute for Science and Technology (Benner was formerly based at the University of Florida) is a pioneer of synthetic biology. He builds models of how life might function using unnatural genetic systems. His argument is simple: There is no reason the limited set of molecules in DNA should be the only form of life that has arisen in the universe and we need models of what other kind of life could be out there. “We can’t think of any transparent reason that these four bases [A, G, C and T] are used on earth,” explains Benner.<sup>105</sup>

Benner has demonstrated that a number of novel biological molecules can be chemically synthesised so that they reproduce and pass on their genetic inheritance in the same way that DNA does. He sees artificial genetics as a way to explore basic questions, such as how life got started on earth, how it evolves and even what forms it may take elsewhere in the universe.

Almost two decades ago, Benner led a team that created DNA containing two artificial nucleotide bases in addition to the four that appear in life as we know it. Later Benner was able to show that it was possible to

increase the number of nucleotides to 12. Benner calls his expanded system of bases AEGIS (An Expanded Genetic Information System) and has commercially licensed it to privately-held EraGen Biosciences of Madison, WI (USA).<sup>106</sup> EraGen produces and sells DNA oligos built from the four natural DNA bases and the additional two artificial ones. The company calls its expanded genetic alphabet “a truly revolutionary molecular diagnostics technology platform” that it uses for the development of new genetic tests such as an assay for Cystic Fibrosis, or the detection of infectious biowarfare agents.<sup>107</sup>

In 2004 Benner further showed that his six-letter DNA-like molecule (including letters ‘K’ and ‘X’) could support the molecular “photocopying” operation known as polymerase chain reaction, in which the molecule copies itself and then directs the synthesis of copies of copies. Since natural polymerase enzymes rejected his artificial base pairs, Benner was forced to design a new, compatible version of the enzyme polymerase.<sup>108</sup>

“Considering how hard we had to work to get Earth polymerases to accept our artificial DNA, we doubt that our artificial DNA would survive for an instant outside of the laboratory on this planet,” explains Benner.<sup>109</sup> “But a six-letter DNA might support life on other planets, where life started with six letters and is familiar with them. Or even DNA that contains up to 12 letters, which we have shown is possible.”<sup>110</sup>

Building on Benner’s pioneering work, a number of other synthetic biologists are developing practical

*“We’re trying to expand the genetic code.”*

— Dr. Floyd E. Romesburg, Scripps Research Institute

*“I suspect that, in five years or so, the artificial genetic systems that we have developed will be supporting an artificial life-form that can reproduce, evolve, learn and respond to environmental change.”*

— Steven Benner, Westheimer Institute for Science and Technology

***“We’ve designed a genetic system that’s completely new and unlike any living system on Earth.”***

— Eric T. Kool, Stanford University

applications for artificial genetic systems. In 2005 Floyd Romesburg, a biochemist at the Scripps Institute in La Jolla, California, added an extra letter F (made from flourobenezene) to the existing four bases that occur naturally in DNA, and successfully created an enzyme that can make the modified biomolecules self-replicate.

Stanford University chemist Eric T. Kool has re-designed the existing base pair A and T to be larger – creating an expanded double helix that glows in the dark and is unusually stable at higher temperatures. Kool dubbed his new molecule xDNA (for expanded DNA): “We’ve designed a genetic system that’s completely new and unlike any living system on Earth,” announced Kool.<sup>111</sup>

Like Benner, Kool emphasises that expanded DNA will not pose new biosafety risks. “This new DNA couldn’t function in the natural system on Earth,” he asserts. “It’s too big. However, we like to think that

one day it could be the genetic material for a new form of life, maybe here or on another planet.”<sup>112</sup>

Benner and Kool haven’t built their artificial genetic systems into full organisms yet. “I suspect that, in five years or so, the artificial genetic systems that we have developed will be supporting an artificial life-form that can reproduce, evolve, learn and respond to environmental change,” Benner predicted in 2004.<sup>113</sup>

Although Benner and others are confident that artificial genetic systems will not survive outside the lab, research in this field raises profound biosafety questions. Dr. Jonathan King, a professor of molecular biology at MIT told the *New York Times*: “It’s a powerful technology, and like all powerful technologies it needs appropriate oversight and regulation.”<sup>114</sup> One possible scenario he suggested is that proteins with artificial amino acids could elicit allergic reactions if used in drugs or in food.<sup>115</sup>

## Implications of Synthetic Biology:

**I. Building a Better Bio-Weapon – What does synthetic biology mean for bioweapons?**

**II. The New Synthetic Energy Agenda – Rebooting Biofuels**

**III. Synthesizing New Monopolies from Scratch – Synthetic Biology and Intellectual Monopoly**

**IV. Synthetic Conservation – What are the implications of gene synthesis and digital DNA for conserving genetic resources and the politics of biodiversity?**

**V. Synthetic Commodities – Implications For Trade**

**VI. SynBioSafety**

### **I. Building a Better Bio-Weapon – What does synthetic biology mean for bioweapons?**

*“I expect that this technology will be misapplied, actively misapplied and it would be irresponsible to have a conversation about the technology without acknowledging that fact.” – Drew Endy, Synthetic Biologist, MIT<sup>116</sup>*

First there was polio. In 2002 a team of researchers at the State University of New York at Stony Brook, led by molecular geneticist Dr. Eckard Wimmer, mail-ordered short sequences of synthetic DNA strands (oligonucleotides) and pasted them together into a functional version of poliovirus. (The researchers injected their *de novo* virus into some unlucky mice for confirmation that the pathogen “worked.”)<sup>117</sup> When this extreme genetic engineering feat was announced to the world, Wimmer and his team were attacked as irresponsible and told that their published work could potentially show terrorists how to make a bio-weapon. According to Wimmer, the point of undertaking the experiment was to illustrate that it was possible to construct such a dangerous pathogen using mail-order parts.<sup>118</sup>

“This is a wake up call,” he told the *Washington Post* in July 2006.<sup>119</sup>

In the same interview Wimmer revealed that he has repeated his poliovirus reconstruction a further six times and each time the work is easier and faster.<sup>120</sup>

Then there was the flu. The strain of avian influenza that jumped to humans early in the last century (H1N1), sometimes known as “The Spanish Flu,” killed somewhere between 20 and 50 million people worldwide in 1918-1919 – a higher death toll than all of World War I.<sup>121</sup> Despite the lethal nature of the highly communicable virus, efforts to reconstruct it began in the 1950s. (By that time the H1N1 strain was eradicated from the earth – having disappeared with its last victims.) In 1997, Dr. Jeffrey Taubenberger of the US Armed Forces Institute of Pathology in Washington, DC succeeded in recovering and sequencing fragments of the viral RNA from preserved tissues of 1918 flu victims buried in the Alaskan permafrost.<sup>122</sup> Eight years later, Taubenberger’s team and collaborating researchers at Mount Sinai School of Medicine in New York and the US Centers of Disease Control (CDC) in Atlanta

*“I expect that this technology will be misapplied, actively misapplied...”*

— Drew Endy, MIT

**“This is extremely foolish.”**

Bill Joy and Ray Kurzweil, commenting in the *New York Times* on the publication of the 1918 flu virus genome in a public database

**Today’s synbio industry has made the work of bioweaponers a whole lot easier.**

announced that they had resurrected the lethal virus. They published details of the completed genome sequencing in *Nature* and details of the virus recreation in *Science*.<sup>123</sup> About ten vials of the flu virus were produced with the possibility that more could be made to accommodate research needs, according to the CDC scientist who inserted the virus into a living cell, the last step in its reconstruction.<sup>124</sup> Craig Venter later described the resurrection of the 1918 flu virus as “the first true Jurassic Park scenario.”<sup>125</sup>

Scientists responsible for reconstructing the 1918 flu virus may have benefited from publications in high profile, peer-reviewed journals and increased funding, but enthusiasm for their work is not universal. “Genetic characterization of influenza strains has important biomedical applications. But it is not justifiable to recreate this particularly dangerous eradicated strain that could wreak havoc if released, deliberately or accidentally,” admonished biologist Jan van Aken of the bioweapons watchdog group, the Sunshine Project, back in 2003.<sup>126</sup> In a ‘post-reconstruction’ opinion piece in the *New York Times*, two leading technology thinkers, Bill Joy and Ray Kurzweil, took the CDC to task for publishing the full genome of the 1918 flu virus in the GenBank database: “This is extremely foolish,” they wrote.<sup>127</sup> “The genome is essentially the design of a weapon of mass destruction. No responsible scientist would advocate publishing precise designs for an atomic bomb...revealing the sequence for the flu virus is even more dangerous.”<sup>128</sup>

State-sponsored biowarfare programmes are known to have gone

the synbio route in the past, even when the road was much rougher and longer than it is today. In a 2006 interview with *Technology Review*, Serguei Popov, who genetically engineered bioweapons for the Soviet Union’s secret biowarfare programme, explained that over 25 years ago, he “had fifty people doing DNA synthesis manually, step by step” to create biologically active viruses.<sup>129</sup> “We had no DNA synthesizers then,” he says. “One step was about three hours, where today, with the synthesizer, it could be a few minutes – it could be less than a minute. Nevertheless, already the idea was that we would produce one virus a month.”<sup>130</sup>

Today’s synbio industry has made the work of bioweaponers a whole lot easier. Richard H. Ebright, a biochemist at Rutgers University, clarified for *The Washington Post* that it would now be possible and “fully legal for a person to produce full-length 1918 influenza virus or Ebola virus genomes, along with kits containing detailed procedures and all other materials for reconstitution...it is also possible to advertise and to sell the product...”<sup>131</sup> Eckard Wimmer is even more blunt about the potentially deadly combination of accessible genomic data and DNA-synthesizing capabilities: “If some jerk then takes the sequence of [a dangerous pathogen] and synthesizes it, we could be in deep, deep trouble.”<sup>132</sup>

In June 2006, *The Guardian* (UK) announced that one of its journalists ordered a fragment of synthetic DNA of *Variola major* (the virus that causes smallpox) from a commercial gene synthesis company and had it delivered to his residential ad-

dress.<sup>133</sup> The genome map of *Variola major* is available on the Internet in several public databases. Smallpox is a highly infectious disease that hasn't been around for almost 30 years, with the most recent natural case occurring in Somalia in 1977, according to the CDC. With approximately 186,000 base pairs, a commercial outfit could theoretically crank out the entire DNA for a synthetic version of *Variola major* in less than two weeks, for about the price of a high-end sports car.<sup>134</sup> The company involved in *The Guardian's* investigation, VH Bio Ltd., based in Gateshead, UK, did not screen the requested sequence against the known genome sequences of dangerous microorganisms, a precautionary (though voluntary) measure to hinder malicious use.<sup>135</sup> An earlier investigation by *New Scientist* found that only five of twelve DNA synthesis companies systematically checked their orders to ensure that they were not synthesizing and delivering DNA fragments that could be used to assemble the genome of a dangerous pathogen<sup>136</sup> or the genome of a new "chimera" virus (that is, a combo-organism made from two different pathogens), with increased lethality and/or resistance to known treatments. It is even possible that a chimera organism made from benign sources of DNA could turn out to be pathogenic.

But concerns about synbio's bio-weaponry potential are not limited to the construction or reconstruction of virulent microorganisms. Work in the area of pathway engineering is allowing synthetic biologists to construct the genetic networks that code for particular proteins and these synthetic net-

works can then be inserted into microbial hosts such as *E. coli* or yeast. (See Pathway Engineering, p. 19.) Microbes could function as "biofactories" to produce natural protein poisons such as snake, insect and spider venoms, plant toxins and bacterial toxins such as those that cause anthrax, botulism, cholera, diphtheria, staphylococcal food poisoning and tetanus.<sup>137</sup> In addition, biowarfare experts are concerned that protein engineering could be used to create hybrids of protein toxins.<sup>138</sup> A 2003 declassified CIA document from the US, entitled "The Darker Bioweapons Future," acknowledges that, "Growing understanding of the complex biochemical pathways that underlie life processes has the potential to enable a class of new, more virulent biological agents engineered to attack distinct biochemical pathways and elicit specific effects...The same science that may cure some of our worst diseases could be used to create the world's most frightening weapons."<sup>139</sup>

The proliferation of synbio techniques means that the threat of bioterror (or bioerror, as Martin Rees, the UK's Astronomer Royal, has called an unintentional but nonetheless deadly biotech mishap)<sup>140</sup> is constantly evolving, challenging the abilities of the international Biological and Toxin Weapons Convention (BWC) and civil society weapons-watchdogs to monitor and prevent biowarfare. Synbio's rapidly changing nature will also affect the way that nations conduct war. Drew Endy, one of the leaders in the field of synthetic biology, has warned about what he calls "the remilitarization of biology"<sup>141</sup> that could follow from developments in synbio-technologies.

**"If some jerk then takes the sequence of [a dangerous pathogen] and synthesizes it, we could be in deep, deep trouble."**

— Dr. Eckard Wimmer, molecular biologist who led the team that synthesized poliovirus

***Synbio will also affect the way that nations conduct war.***

*The same science that may cure some of our worst diseases could be used to create the world's most frightening weapons."*

— CIA report, "The Darker Bioweapons Future"

*Syn-biologists can whip up virtually any toxin they want from scratch, and the DNA sequences in their potentially lethal products may or may not look identical to the sequences we know to occur naturally.*

#### **Box 4: NSABB: Scientific Advice on How to Throw Out the Baby with the Bath Water**

The US CDC maintains a list of about eighty "select agents" (SAs) and toxins that pose a severe threat to public health and safety and whose possession, use and distribution are controlled by law, known as the Select Agent Rules.<sup>142</sup> The SA list includes, for example, bovine spongiform encephalopathy (BSE) agent, Ebola, Lassa fever, Marburg, Foot-and-mouth disease, reconstructed 1918 influenza and *Variola major* viruses as well as *botulinum* neurotoxins. However, these restrictions appear to apply to possession, use and distribution of physical agents only, not related genomic data. In light of the challenges posed by emerging synbio-technologies, the US's National Science Advisory Board for Biosecurity (NSABB) established a "Synthetic Genomics Working Group" in November 2005 to deal with research that is unclassified.

The WG articulated some real-world concerns ushered in by the era of synthetic biology, such as the ease with which "individuals versed in, and equipped for routine methods in molecular biology can use regularly available starting material and procedures to derive some SAs *de novo*" and that synthetic biology now "allows expression of agents that resemble and have the attributes of specific Select Agent(s), without being clearly identifiable as SA based on the sequence." In other words, syn-biologists can whip up virtually any toxin they want from scratch, and the DNA sequences in their potentially lethal products may or may not look identical to the sequences we know to occur naturally. To put it another way, the reality of the synbio age is that conventional taxonomies of dangerous substances cannot be comprehensive.

Based on this observation, the WG draws a reasonable conclusion – that regulators should "re-evaluate reliance upon a finite list of agents as the foundation for the oversight framework." Unfortunately, even shockingly, the observation led the WG to *weaken* current regulation by recommending repeal of the law that makes it illegal to produce, engineer, synthesise or acquire a virus containing 85% or more of the genetic sequence of *Variola major* (the smallpox agent).<sup>143</sup> The Working Group's recommendation to repeal US law 18 U.S.C. 175(c) was unanimously approved by the Board. The Sunshine Project describes the Board's dangerous decision in this way:

"Synthetic biology may be new; but challenges to taxonomic conventional wisdom are not. Evolution happens...The novel possibilities of synthetic biology are thus not without precedent in nature, in the sense that taxonomy is always encountering the difficult-to-classify and is currently incapable of fully describing naturally occurring diversity. No matter what is cooked up in a synthetic biology lab, that doesn't change the fact that there are diseases out there that can kill you. Scientists know what most of them are, and can reasonably define them. Hence the need for the Select Agent Rule is unaltered by the powers to manipulate, even create, dangerous forms of life (and nucleic acids) that is possibly offered by synthetic biology."<sup>144</sup>

## II. The New Synthetic Energy Agenda – Rebooting Biofuels

*“Something I’m really excited about are the synthetic biology projects they’re working on to create new kinds of fuels so we can reduce our dependence on oil and protect our environment.”* – Arnold Schwarzenegger, Governor of California<sup>146</sup>

When genetically modified organisms were first commercialised in the mid 1990s the controversy was largely focused on agriculture and food. A decade later, as fledgling companies seek to move synthetic organisms from lab to marketplace, agriculture is once again on center stage – only this time the spotlight isn’t shining on agri-food, but on agri-energy.

Synthetic biology’s promoters are hoping that the promise of a very “green” techno-fix – synthetic microbes that manufacture biofuels cheaply or put a chill on climate change – will prove so seductive that the technology will win public acceptance despite its risks and dangers.

In his 2006 State of the Union address, US President George W. Bush announced that his government would devote “additional research funds for cutting-edge methods of producing ethanol, not just from corn, but from wood chips and stalks or switchgrass.”<sup>147</sup>

Synthetic biology is one of the “cutting-edge” methods for biofuel production alluded to by President Bush. That part of his speech was written a few days earlier by Aristides Patrinos, then-associate director of the US Department of Energy’s (DOE) Office of Biological and Environmental Research.<sup>148</sup>

At the DOE, Patrinos had overseen both the Human Genome Project and more recently the Genomes to Life (GTL) programme – which supports research to focus synthetic biology on the production of biofuels such as ethanol and hydrogen. The GTL programme also promotes research on technological fixes such as carbon sequestration to mitigate climate change.<sup>149</sup>

Two months after Bush’s speech, Patrinos left the Department of Energy to take up a new post as president of Craig Venter’s new company, Synthetic Genomics, Inc. The company aims to use microbial diversity collected from seawater samples as the raw material to create a new synthetic microbe – one that is engineered to accelerate the conversion of agricultural waste to ethanol.

Patrinos is one of many high-profile industrialists and senior scientists who are climbing aboard the biofuels bandwagon. Bill Gates, for example, the soon-to-be retired chairman of Microsoft, recently bought 25% of Pacific Ethanol, while his Microsoft co-founder Paul Allen has invested in Imperium Renewables, a Seattle-based company that will produce ethanol mainly from soybeans and canola oil. Richard Branson, chairman of the Virgin Group of companies, is devoting \$400 million to ethanol investment while Vinod Khosla, co-founder of Sun Microsystems and partner at Kleiner Perkins, a venture capital firm that famously backed AOL, Google and Amazon,<sup>150</sup> now has a string of investments in ethanol companies. (See below.)

The growing enthusiasm for biofuels in the US stems in part from a

*“We think this area [Synthetic Genomics] has tremendous potential, possibly within a decade, to replace the petrochemical industry.”*

— Craig Venter speaking at Synthetic Biology 2.0<sup>145</sup>

*Synthetic biology’s promoters are hoping that the promise of a very “green” techno-fix will prove so seductive that the technology will win public acceptance despite its risks and dangers.*



*The surging demand for home-grown biofuels won't be easily met by current technologies.*

*In fact, every bushel of corn grown in the US consumes between a third and a half-gallon of gasoline – making it a costly and inefficient feedstock for alternative energy.*

belated recognition that petroleum supplies in “volatile” parts of the world may not be so easily acquired through trade deals or wars. It also deflects attention from tougher tasks like cutting energy consumption and promoting conservation. The current buzz phrase for ethanol is “energy independence.” A typical articulation comes from a Department of Energy report called *From Biomass to Biofuels*: “A robust fusion of the agricultural, industrial biotechnology, and energy industries can create a new strategic energy independence and climate protection.”<sup>151</sup>

In addition to the energy independence mantra, environmental groups such as Natural Resources Defense Council (NRDC) are championing the development of certain types of ethanol as a climate-friendly fuel that could reduce global emissions of carbon dioxide (CO<sub>2</sub>).<sup>152</sup>

The US government’s Energy Policy Act of 2005 requires that 4 billion gallons of ethanol per annum be mixed with gasoline at the pumps – that requirement will rise to 7.5 billion gallons by 2012.<sup>153</sup> (A gallon equals 3.79 litres.) Spurred by lavish government subsidies and growing enthusiasm for “energy independence,” over 100 ethanol refineries were operating in the USA as of mid-2006, producing nearly 5 billion gallons of ethanol.<sup>154</sup>

The biofuel buzz is about to become a boom because the US government mandates that at least 30 percent of fuel for transport be derived from biofuels (mostly ethanol) by 2030 – a goal that would require roughly 60 billion gallons of ethanol to be produced per year.<sup>155</sup> Ford, Daim-

lerChrysler and General Motors together aim to sell over 2 million ethanol-burning cars in the next decade and the world’s largest retailer, Wal-Mart, is mulling plans to sell an ethanol fuel at its 380 US superstores.<sup>156</sup> The ethanol boom is especially good news for giant agro-industrial corporations such as Archer Daniels Midland (ADM), which controls about 30 percent of the US-based ethanol market.<sup>157</sup>

But the surging demand for home-grown biofuels won't be easily met by current technologies. Fuel ethanol can be produced in two ways: The first is by breaking down agricultural starches into sugar, which is then fermented into ethanol. In Brazil ethanol is processed from sugar cane; in the US the primary feedstock is corn. Growing corn and other food/feed crops for ethanol will divert huge amounts of land, water and energy-intensive inputs away from food production to fuel production. But even then, production levels would fall short of US targets. The US Department of Energy calculates that if all corn now grown in the US were converted to ethanol, it would satisfy only about 15 percent of the country’s current transportation needs. Others put that figure as low as 6 percent.<sup>158</sup> But US corn production is energy intensive, requiring massive inputs of fossil fuels for fertilisers, pesticides, tractors, post-harvest processing and transport (and corn must be replanted every year unlike sugar cane, which is a perennial crop that produces for 3-6 years before being replanted). In fact, every bushel of corn grown in the US consumes between a third and a half-gallon of gasoline<sup>159</sup> – making it a costly and

inefficient feedstock for alternative energy.

A second approach is to produce ethanol from cellulose, the fibrous material found in all plants. Cellulosic ethanol can be made from any leftover plant materials, including woodchips, rice hulls, grasses (such as switchgrass and miscanthus) and straw. There are abundant sources available for cellulosic ethanol, as leaves and stalks – normally considered waste – could become feedstocks.<sup>160</sup> Processing ethanol from cellulose has the potential to squeeze at least twice as much fuel from the same area of land as corn ethanol, because much more biomass is available per acre. Miscanthus for example, a perennial grass native to China yields approximately 3,000 gallons of cellulosic ethanol per acre.<sup>161</sup> (One acre is approximately 0.4 hectares.)

If it sounds too good to be true – that’s because it is. It takes a lot of energy to break down cellulose – much more energy, in the form of heat or steam or pressure, than is gained – especially once transport and other lifecycle considerations are factored in. A 2005 study by David Pimentel (Cornell University) and Tad Patzek (University of California Berkeley) examines energy output of biofuels compared with energy input for ethanol production.<sup>162</sup> They found that switchgrass requires 45 percent more fossil energy than the fuel produced, and wood biomass requires 57 percent more fossil energy than the fuel produced. According to Pimentel, “There is just no energy benefit to using plant biomass for liquid fuel. These strategies are not sustainable.”<sup>163</sup>

GMOs haven’t solved the energy equation either. An Ottawa-based company, Iogen, has genetically modified a tropical fungus to produce enzymes that break down cellulose, but it will cost five times more to build its planned biofuel refinery than to build a conventional corn ethanol processing plant.<sup>164</sup> The hunt is on for a better microbe that will cheaply and efficiently break down cellulose to sugars and then ferment those sugars into ethanol – without costing energy. That’s where synthetic biology comes in.

The synthetic biology approach is to custom design a microorganism that can perform multiple tasks, incorporating built-in cellulose-degrading machinery, enzymes that break down glucose, and metabolic pathways that optimise the efficient conversion of cellulosic biomass into biofuel.<sup>165</sup> Aristides Patrinos of Synthetic Genomics describes the all-in-one approach: “The ideal situation would essentially just be one big vat, where in one place you just stick the raw material – it could be switch grass – and out the other end comes fuel...”<sup>166</sup>

Scientists haven’t managed to come up with a designer organism that can do it all, but they are taking steps in that direction. A team from the University of Stellenbosch (South Africa), collaborating with engineering professor Lee Lynd at Dartmouth University (USA), has engineered a yeast that can survive on cellulose alone, breaking down the plant’s cell walls and fermenting the derived sugars into ethanol.<sup>167</sup> Meanwhile, Lynd’s group at Dartmouth is working with a modified bacterium that thrives in high-temperature environments and pro-

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*If any of these synbio approaches to biofuels is successful, the agricultural landscape could quickly be transformed.*

*The rush to plant energy crops in the global South threatens to shift marginal land away from food production, a trend that could introduce new monocultures and compromise food sovereignty.*

duces only ethanol in the process of fermentation.<sup>168</sup> Lynd hopes to commercialise his technology at a start-up company called Mascoma in Cambridge, Massachusetts (USA).<sup>169</sup> Chairing Mascoma's board of directors is venture capitalist and ethanol evangelist, Vinod Khosla, who recently snapped up Cargill's head of biotechnology, Doug Cameron, as his chief scientific advisor. Khosla also funds another synthetic biology energy company known as LS9, based in the San Francisco Bay area (CA, USA).<sup>170</sup>

At Purdue University's Energy Center, Senior Research Scientist, Dr. Nancy Ho, has developed a modified yeast that can produce 40 percent more ethanol from biomass than naturally occurring yeast, and she is now working with petroleum companies to convert straw into fuel.<sup>171</sup> The Nobel Prize-winning head of the prestigious Lawrence Berkeley Lab, Dr. Steven Chu, grabbed headlines last year when he suggested that synthetic biology could be used to rewire the genetic networks in a cellulose-crunching bug found in the gut of termites.<sup>172</sup> As a first step, the Berkeley Lab is sequencing microorganisms living in the termite's gut, to identify genes responsible for degrading cellulose.

If any of these synbio approaches is successful, the agricultural landscape could quickly be transformed as farmers plant more switchgrass or miscanthus – not only in North America, but also across the global South. The US DOE considers cellulosic ethanol a “carbon neutral” fuel source<sup>173</sup> (meaning that the amount of CO<sub>2</sub> absorbed in growing the plants that produce the biomass

roughly equals the amount of CO<sub>2</sub> produced in burning the fuel. But these “carbon offset” calculations are controversial because they are difficult, if not impossible, to substantiate).<sup>174</sup> Deeming cellulosic ethanol carbon neutral, however, will likely mean that it will qualify as a Clean Development Mechanism (CDM) activity under the Kyoto Protocol – a scheme established to reward polluting companies with emissions credits if they invest in “clean energy” projects in the global South.<sup>175</sup> Civil society critics regard CDM as industry “greenwashing,” a publicly subsidised scheme that will not combat climate change or diminish its causes.<sup>176</sup> Under the CDM, Northern industries that grow large plantations of energy crops in the South can be allowed to offset these projects against their emissions. Of the 408 registered CDM activities as of mid-November 2006, 55 are described as biomass energy projects. India serves as “host country” for 32 of the 55 projects.<sup>177</sup>

The rush to plant energy crops in the global South threatens to shift marginal land away from food production, a trend that could introduce new monocultures and compromise food sovereignty. At SynBio 2.0, the May 2006 conference held at Berkeley, Dr. Steven Chu noted that there is “quite a bit” of arable land suitable for rain-fed energy crops, and that Latin America and Sub-Saharan Africa are areas best suited for biomass generation.<sup>178</sup> The 2005 US Energy Act mandates the US State Department to transfer climate-friendly technologies (“greenhouse gas intensity reducing technologies”) to developing countries,<sup>179</sup> a move that could increase

pressure on already scarce or depleted soil and water resources if it involves large-scale production of energy crops. A 2006 report by the Sri Lanka-based International Water Management Institute (IWMI) warns that growing crops for biofuel could worsen water shortages: “If people are growing biofuels and food it will put another new stress. This leads us to a picture of a lot more water use,” explained David Molden of IWMI.<sup>180</sup> By removing biomass that might previously have been returned to the soil, fertility and soil structure would also be compromised.<sup>181</sup> As presently envisioned, large-scale, export-oriented biofuel production in the global South will have negative impacts on soil, water, biodiversity, land tenure and the livelihoods of peasant farmers and indigenous peoples.

Growing demand for energy, and the shift from food to fuel production, could increase the energy sector’s influence in agricultural policies. It could also mean a new wave of consolidation in the form of mergers and strategic alliances between agribusiness and energy corporations. The Department of Energy’s roadmap for developing synthetic biology technologies for ethanol production notes: “This research approach will encourage the critical fusion of the agriculture, industrial biotechnology, and energy sectors.”<sup>182</sup> In a recent press release on its biofuels strategy, ADM’s CEO Patricia Woertz claims that her company is “uniquely positioned at the intersection of the world’s increasing demands for both food and fuel. As one of the largest agricultural processors in the world and the largest biofuels producer in the

world, ADM is in a category of one to capitalize on the exceptional opportunity ahead.”<sup>183</sup>

But converting plant biomass to fuel isn’t the only way that synbio could upend the energy sector. Craig Venter’s 2-year microbe-collecting expedition netted previously unknown species of bacteria that capture sunlight with photoreceptors and convert it into chemical energy.<sup>184</sup> Since photosynthesis is capable of producing minute levels of hydrogen, Venter’s team is exploring the idea of altering photosynthesis in cells to produce hydrogen.

University of California professor Jay Keasling, founder of Amyris Biotechnologies, wants to design an organism that produces a fuel similar to gasoline. “Ethanol has a place, but it’s probably not the best fuel in the long term,” Keasling told *Technology Review*. “People have been using it for a long time to make wine and beer. But there’s no reason we have to settle for a 5,000-year-old fuel.”<sup>185</sup> Amyris recently hired John Melo, former president of US Fuels Operations for BP, as its new chief executive. “It even sounds amazing to us what we are trying to do,” said Jack Newman, a co-founder of Amyris and vice president of research. “Basically, we are taking the modern principles of synthetic biology and trying to replace crude oil.”<sup>186</sup>

The US military also wants to use synthetic biology for energy production. The US government’s Defense Advanced Research Projects Agency (DARPA) is funding a collaboration between Richard Gross of Polytechnic University (New York) and gene synthesis company DNA 2.0 (Silicon Valley, California) to develop a new

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*Over the past quarter century, vigorous and unbridled patent activity in the field of biotech has paved the way for a me-too approach in synthetic biology.*

*Patents have already been granted on many of the products and processes involved in synthetic biology.*

kind of energy-rich plastic that can be used first for packaging and then reused as fuel. DNA 2.0 aims to synthetically design the enzymes to produce the polymer. The company claims that soldiers in the field will be able to burn the plastic that wraps their supplies, recovering 90% of the energy as electricity.<sup>187</sup>

### **III. Synthesizing New Monopolies from Scratch – Synthetic Biology and Intellectual Monopoly**

Over the past quarter century, vigorous and unbridled patent activity in the field of biotech has paved the way for a me-too approach in synthetic biology. *Diamond vs. Chakrabarty*, the 1980 US Supreme Court case that opened the door to the patenting of all biological products and processes, easily extends to synthetic biology. In language that perfectly describes today's synthetic organisms, the 1980 Court determined that, "...the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature's handiwork, but his own: accordingly it is patentable subject matter."<sup>188</sup> Unaltered genetic material in its natural environment is not patentable, but once isolated, modified, purified, altered or recombined, genetic material – including synthetic DNA – becomes fair game for monopoly patent claims (provided patent examiners deem that it meets the criteria of novelty, utility and non-obviousness).

Synthetic biology is inspired by the convergence of nanoscale biology/biotech, engineering and

computing. And that means intellectual property claims related to synthetic biology involve not just nanoscale DNA synthetically produced – but computers and software as well. Duke University (North Carolina, USA) law professors Arti Rai and James Boyle point out that biotech and software have proven ambiguous and problematic areas for intellectual property law – a situation that could create the "perfect storm" for synthetic biology.<sup>189</sup>

Patents have already been granted on many of the products and processes involved in synthetic biology (see Table 1, p. 35). Examples include:

- Patents on methods of building synthetic DNA strands<sup>190</sup>
- Patents on synthetic cell machinery such as modified ribosomes<sup>191</sup>
- Patents on genes or parts of genes represented by their sequencing information<sup>192</sup>
- Patents for the engineering of biosynthetic pathways<sup>193</sup>
- Patents on new and existing proteins and amino acids<sup>194</sup>
- Patents on novel nucleotides that augment and replace the letters of DNA<sup>195</sup>

Some of these patents cast an extremely wide net. For example, US Patent 6,521,427, issued to Glen Evans of Egea Biosciences (a California-based subsidiary of pharmaceutical giant Johnson & Johnson) includes broad claims on a method for synthesizing entire genes and networks of genes comprising a genome, as the 'operating system' of living organisms – potentially a description of the entire synthetic biology en-

deavour.<sup>196</sup> Other patents awarded to Jay Keasling and his colleagues at Berkeley's synthetic biology lab cover methods for inserting artificial metabolic pathways into bacteria and testing them for expression of new compounds.<sup>197</sup>

Patents can be granted on the genetic networks or 'circuitry' that synthetic biologists have isolated from nature and on the distinct functional parts or units that make up those circuits – whether they function as genetic switches, oscillators or molecular 'gates.' MIT's non-profit Registry of Standard Biological Parts was created as a communal repository for sharing, using, and improving on the interchangeable modules – the BioBricks – that can be assembled to create biological systems in living cells. However, MIT's Drew Endy estimates that about one-fifth of the biological functions encoded by parts of BioBricks are already covered by patent claims (held by individuals and organizations not associated with MIT's BioBricks project).<sup>198</sup>

There are also patents on classes of naturally occurring biomolecules commonly used as tools in synthetic biology. One example is 'zinc fingers,' a family of proteins found in nature that are used by synthetic biologists because they bind to targeted sequences of DNA. An article in *Nature* describes multiple patents held by Sangamo Biosciences as a "stranglehold" on zinc finger technologies, their uses in drug discovery and the regulation of gene expression.<sup>199</sup> MIT and Scripps Research Institute also hold patents on zinc fingers.

In addition to property claims on

the wetware of life, synthetic biologists have also expressed concern that broad concept-level patents have been secured on the computer systems and software they use routinely.<sup>200</sup> Such systems are used to design genetic circuits *in silico* before synthesizing DNA *in vivo*. US Patent 5,914,891 owned by Stanford University describes genes as 'circuits' and claims: "A system and method for simulating the operation of biochemical networks [that] includes a computer having a computer memory used to store a set of objects, each object representing a biochemical mechanism in the biochemical network to be simulated."<sup>201</sup> If enforced, such broad claims could create a gatekeeper-like monopoly on the field of synthetic biology, which requires massive computation and computer memory to carry out the synthesis and design of DNA networks.

In their article on synthetic biology and intellectual property, Duke University law professors Rai and Boyle cite the example of broad foundational patents such as US Patent 6,774,222, entitled "Molecular Computing Elements, Gates and Flip-flops," issued to the US Department of Health and Human Services in 2004.<sup>202</sup> The patent involves DNA logic devices that operate in a manner analogous to their electronic counterparts – for both computation and control of gene expression.

Rai and Boyle explain the far-reaching scope of the patent:

"The patent covers the combination of nucleic-acid binding proteins and nucleic acids to set up data storage, as well as logic gates that perform basic Boolean algebra. The patent

*Synthetic biologists have also expressed concern that broad concept-level patents have been secured on the computer systems and software they use routinely.*

***“Overly restrictive licensing and smotheringly broad patent interpretations could make a shambles of synthetic biology.”***

— Editorial, *Scientific American*

***It remains to be seen if open source proponents can counter a corporate-dominated science and technology that thrives on aggressive patenting activity.***

notes that the invention could be used not only for computation but also for complex (‘digital’) control of gene expression. The broadest claim, claim 1, does not limit itself to any particular set of nuclei-acid binding proteins or nucleic acids. Many types of molecular computing and control of gene expression are likely to be covered by such a patent. Moreover, the claim uses language that would cover not only the ‘parts’ that performed the Boolean algebra but also any device and system that contained these parts. Such a patent would seem effectively to patent algebra, or the basic functions of computing, when implemented by the most likely genetic means. It is difficult even to imagine the consequences of an equivalent patent on the software industry.”<sup>203</sup>

While some gene synthesis companies screen their product orders for potentially dangerous sequences, it seems that no company screens sequences for possible patent infringement. Jeremy Minshull, of DNA2.0, told the attendees at the SynBio2.0 conference in Berkeley that his company specifically disclaims responsibility for patent infringement in the event that an ordered sequence includes patented material. Minshull explained that screening for patented sequences would require a company to keep a team of 50 lawyers on the payroll, an expense that would be reflected in the market price of DNA: the price would be closer to \$100 per base rather than “a buck a base.”<sup>204</sup>

In May 2006 the editors of *Scientific American* warned that “overly restrictive licensing and smotheringly broad patent interpretations could

make a shambles of synthetic biology.”<sup>205</sup> Many practitioners in the fledgling field agree, and there is ongoing discussion about the pros and cons of a “conceal or reveal” approach to synbio.<sup>206</sup> Some advocate for an “open source” strategy, mimicking the free software movement in computing. Drew Endy and his former colleague Rob Carlson first coined the term “open source biology” while at Berkeley’s Molecular Sciences Institute in the late 1990s<sup>207</sup> and both continue to promote the idea as an integral part of their vision for synthetic biology. Their model is Linux – the non-proprietary computer operating system that hundreds of thousands of programmers developed voluntarily, building on each other’s work and releasing their improved source code back to common ownership. Endy ensures that all his lab work is made public on a wiki (publicly editable web pages) and makes the sharing of genetic sequences a cornerstone of MIT’s Registry of Standard Biological Parts.

Endy and some of his colleagues dislike the practice of patenting things found in nature (“It makes me physically angry,” claims Endy).<sup>208</sup> By designing genetic code into abstracted ‘BioBricks’ that easily snap together, Endy believes it will someday be possible for anyone to participate in the design of synthetic organisms. He imagines a new class of professionals similar to today’s graphic designers that will design new biological devices on laptops and then send those designs by email to gene foundries.<sup>209</sup>

Nevertheless, synthetic biologists like Endy are also entrepreneurs. Codon Devices, Inc., the synbio

**Table 1: A Sample of Recent Synthetic Biology Patents**

Inventor	Patent / Application Number	Publication Date	Description
Steven Benner	US 6,617,106	9 September 2003	Methods for preparing oligonucleotides containing non-standard nucleotides
Steven Benner	US20050038609A1	17 Feb. 2005	Evolution-based functional genomics
Steven Benner	US 5,432,272	11 July 1995	Method for incorporating into a DNA or RNA oligonucleotide using nucleotides bearing heterocyclic bases
Harry Rappaport (Assignee: Temple University)	US 5,126,439	30 June 1992	Artificial DNA base pair analogues
George Church, Brian Baynes (Assignee: Codon Devices, Inc.)	WO06076679A1	20 July 2006	Compositions and methods for protein design
George Church, Jingdong Tian (Assignee: Harvard)	US20060127920A1	15 June 2006	Polynucleotide synthesis
Noubar Afeyan, et al. (Assignee: Codon Devices, Inc.)	WO06044956A1	27 April 2006	Methods for assembly of high fidelity synthetic polynucleotides
Jay Keasling, et al.	US20040005678A1	8 Jan 2004	Biosynthesis of amorpha-4,11-diene (in a host cell, useful as pharmaceuticals)
Jay Keasling, et al.	US20030148479A1	7 August 2003	Biosynthesis of isopentenyl pyrophosphate (in a host microorganism, useful for pharmaceutical purposes)
Keith K. Reiling, et al. (Assignee: University of California)	WO05033287A3	14 April 2005	Methods for identifying a biosynthetic pathway gene product
Ho Cho, et al. (Assignee: Ambrx, Inc.)	WO06091231A2	31 August 2006	Biosynthetic polypeptides utilizing non-naturally encoded amino acids
Robert D. Fleischmann, J. Craig Venter, et al. (Assignee: Human Genomes Sciences, Johns Hopkins Univ.)	US20050131222A1	16 June 2005	Nucleotide sequence of the <i>haemophilus influenzae Rd</i> genome, fragments thereof, and uses thereof (genome recorded on computer readable medium - useful for identifying commercially important nucleic acid fragments by homology searching)
Frederick Blattner, et al. (Assignee: Univ. of Wisconsin)	US 6,989,265	24 January 2006	New bacterium with a genome genetically engineered to be at least 5% smaller than the genome of its native parent strain, useful for producing a wide range of commercial products
Glen Evans (Assignee: Egea Biosciences; subsidiary of Johnson & Johnson)	US 6,521,427	18 Feb. 2003	Method for the complete chemical synthesis and assembly of genes and genomes
Jay Keasling, et al.	US20060079476A1	13 April 2006	Method for enhancing production of isoprenoid compounds
James Kirby, et al. (Assignee: Univ. of California)	WO06014837A1	9 Feb. 2006	Genetically modified host cells and use of same for producing isoprenoid compounds
Nigel Dunn-Coleman, et al. (Assignee: Dupont; Genencor)	US 7,074,608	11 July 2006	Method for the production of 1,3-propanediol by recombinant <i>Escherichia coli</i> strain comprising genes for coenzyme B12 synthesis
Eric T. Kool (Assignee: University of Rochester)	US 7,033,753	25 April 2006	Compositions and methods for nonenzymatic ligation of oligonucleotides and detection of genetic polymorphisms

Source: ETC Group



“Pretty soon, we won’t have to store DNA in large refrigerators. We’ll just write it when we need it.”

— Tom Knight, Synthetic Biologist, MIT<sup>211</sup>

company co-founded by Endy in 2005, holds an extensive patent portfolio (63 patent applications and 22 issued patents as of late 2006). The company’s policy is to “aggressively pursue patent protection for most of our proprietary technology, and protect other aspects of our proprietary technology as trade secrets.”<sup>210</sup> Proponents of open source biology seek to facilitate access and collaborative innovation – worthy goals that, unfortunately, do not address the more fundamental controversies surrounding synbio’s development. It also remains to be seen if open source proponents can counter a corporate-dominated science and technology that thrives on aggressive patenting activity.

#### IV. Synthetic Conservation – What are the implications of gene synthesis and digital DNA for conservation of genetic resources and the politics of biodiversity?

*“In the old days, all biology was ‘in vivo’ – in life. Then scientists learned how to grow organisms ‘in vitro’ – in glass. Now biology is ‘in silico.’” – Nathanael Johnson, “Steal This Genome,” East Bay Express.*<sup>212</sup>

#### Storing Diversity Digitally (or Goodbye CGIAR... Hello Google):

When a team of synthetic biologists announced in 2005 that they had successfully resurrected and rebuilt a fully working version of the 1918 flu virus, it foreshadowed the era of electronic biodiversity – digital storage of DNA. Scientists predict that



within a few years it will be easier to synthesise a virus than to request it from a culture collection or find it in nature. Within a decade it may be possible to synthesise bacterial genomes. Existing *ex situ* collections of microbial strains (as well as seeds and animals) rely on the maintenance of biological samples. If DNA can be rapidly sequenced and the code stored digitally *in silico* the potential exists for an organism's genome to be resurrected *in vivo* via synthetic biology. As the price of gene sequencing continues to fall, will cost-cutting bureaucrats be tempted to neglect repositories of the world's collected biodiversity in favor of computer servers, hard drives and a network of gene synthesisers? Will financial support for gene banks and other genetic conservation strategies erode as a result?

Today, members of the World Federation of Culture Collections (WFCC) in 66 countries store over 1.3 million different samples of bacteria, viruses, fungi and other microbes.<sup>213</sup> Given sufficient time and money, virtually any of these samples can be sequenced. If those same samples were stored digitally, DNA molecules of any desired sequence could be downloaded at the click of a mouse anywhere in the world.

The cornerstone of today's digital DNA system is the International Nucleotide Sequence Databases, which includes the European Molecular Biology Laboratory (EMBL) Data Library (UK), the DNA Data Bank of Japan and GenBank (US). The three databases exchange data to maintain a uniform and comprehensive collection of sequence in-

formation. As of October 2006, GenBank, operated by the US National Institutes of Health, has digitally stored over 66 billion nucleotide bases<sup>214</sup> from more than 205,000 named organisms.<sup>215</sup> The number of nucleotide bases recorded in GenBank is doubling approximately every 18 months. As of September 2005 the database included 250 whole microbial genomes, seventy of which had been deposited in the previous 12 months.<sup>216</sup> These are the raw data sources [libraries] from which synthetic biologists can gather DNA sequences to construct new life-forms – just as microbiologists rely on the culture collections of the WFCC and plant breeders rely on a network of gene banks supported by the Consultative Group on International Agricultural Research (CGIAR) such as IRRI (International Rice Research Institute) and CIMMYT (International Maize and Wheat Improvement Center).

DNA databases like GenBank could become as user-friendly as Google. In fact, the titanic search engine has signaled interest in storing all of the world's genomic data in their google-farms (large complexes of servers and hard drives). According to an excerpt from *The Google Story* by *Washington Post* journalist David Vise, this plan was hatched in conversation with synthetic biology pioneer Craig Venter: "We need to use the largest computers in the world," Venter said. "Larry and Sergey [founders of Google] have been excited about our work and about giving us access to their computers and their algorithm guys and scientists to improve the process of analyzing data... Genetic information is going to be the leading edge of informa-

*Scientists predict that within a few years it will be easier to synthesise a virus than to request it from a culture collection or find it in nature.*

*DNA databases could become as user-friendly as Google.*

*“If you wanted to resurrect an extinct bacteria – I could imagine being able to do that in the next decade, but if you wanted to resurrect an extinct dinosaur – that’s still very much in the realm of fantasy.”*

— Drew Endy, MIT <sup>218</sup>

tion that is going to change the world. Working with Google, we are trying to generate a gene catalogue to characterise all the genes on the planet and understand their evolutionary development. Geneticists have wanted to do this for generations...Over time Google will build up a genetic database, analyze it, and find meaningful correlations for individuals and populations.”<sup>217</sup>

The use of DNA samples to recover the genomes of rare or extinct species is also gaining currency. In December 2005 a team led by Hendrik Poinar at McMaster University sequenced 1% of the genome of the iconic woolly mammoth by working with a well-preserved 27,000-year-old specimen from Siberia. His team is now working on the rest of the genome.<sup>219</sup> “While we can now retrieve the entire genome of the woolly mammoth, that does not mean we can put together the genome into organised chromosomes in a nuclear membrane with all the functional apparatus needed for life,” explains Ross MacPhee, a researcher at the American Museum of Natural History who worked on the project.<sup>220</sup>

In November 2006 researchers from Germany’s Max Planck Institute for Evolutionary Anthropology in Leipzig announced that they have sequenced one million base pairs of DNA taken from the bone of a Neanderthal.<sup>221</sup> An archaic human species, the Neanderthal has been extinct for some 30,000 years, but researchers estimate they will have a complete genome, 3.2 billion base pairs in length, in about two years.

“The Frozen Ark,” an international consortium sponsored by 11 molecular biology, zoology and con-

servation organizations, including the International Union for the Conservation of Nature (IUCN), plans to collect, preserve and store DNA and viable cells from animals in danger of extinction.<sup>222</sup> In the next five years the project aims to ‘back up’ the DNA of the 36 species classified as “Extinct in the Wild” by IUCN, and then collect the DNA of 7,000 species that are listed as critically endangered, endangered and vulnerable. While the Frozen Ark admits that it isn’t yet possible to reconstruct an extinct species from DNA specimens, the consortium is putting lots of faith in future technologies: “We cannot predict what may be possible even within the next few decades. It may become possible to use samples to create clones of extinct animals when new methods have been developed. We are well on the way already.”<sup>223</sup>

*“The ability to synthesize functional genes and groups of genes should increase access to genetic materials for all scientists because exchange of actual genetic material will not be necessary. Scientists will be able to synthesize genes from published DNA sequences alone. A positive consequence of this is that a greater number of scientists can have access to genes once their sequences are published. This will impact the use of material transfer agreements and contracts.”* – DOE report on Synthetic Genomics<sup>224</sup>

#### **Star-Trek Biopiracy: New Pathways**

**for Bio-Burglars?** It sounds like something from the TV series Star Trek, but today’s botanists (and biopirates) who collect biological specimens in diversity-rich areas of the South may soon have the option of instantaneously “beaming back” samples to far-away labs without

relying on their checked baggage or overnight courier. The combination of rapid 'lab on a chip' gene sequencing devices with ever faster DNA synthesizers means that it will someday be possible to turn DNA samples into information at one location, beam them digitally to another location and then reconstruct them as physical samples anywhere else on the planet. This opens new pathways for biopiracy.

Paul Oldham of Lancaster University's ESRC Centre for Economic and Social Aspects of Genomics observes: "...the extraction of genetic data has classically depended upon the collection, taxonomic identification and storage of field samples, i.e. within herbaria. However, it is conceivable that technological innovation may one-day permit the *in situ* extraction of genetic material and transfer of data to electronic form without the necessity of the collection, taxonomic identification and storage of field samples."<sup>227</sup>

Over the past 20+ years a piecemeal array of international legal mechanisms and conventions have negotiated controversial rules governing access to biodiversity (including seeds, plants, tissues and microorganisms) and exchange of genetic resources around the globe, built on the legal principle that nations have sovereignty over the genetic resources within their borders. The UN Convention on Biological Diversity (CBD), for example, has devoted thousands of negotiating hours to formulate rules on access to and exchange of genetic materials. (In previous critiques of CBD negotiations, ETC Group has pointed out that, rather than support equitable exchange of genetic resources,

the CBD has merely facilitated *legal* access to the genetic resources and knowledge of indigenous and other traditional peoples, mainly in the South. Although the CBD is a multilateral agreement, it strongly encourages bilateral deal-making and commercial exploitation of biodiversity.<sup>228</sup>) Today, with hundreds of thousands of DNA sequences being downloaded daily from genomic databases such as GenBank or EMBL, the CBD's existing rules may become even less relevant for governing access to and exchange of biodiversity: The CBD does not take into account digital transmission of biological materials.

Researchers who access genebanks, such as those held in the CGIAR system, are currently required to sign a legally binding Material Transfer Agreement, but the same researcher can obtain digital DNA sequences from GenBank practically anonymously with no legal strings attached, unless the accession is claimed separately by a patent. (A Material Transfer Agreement [MTA] is a contract that governs the transfer of research materials from one party to another when the recipient intends to use them for his or her own research purposes. The MTA defines the rights of the provider and the recipient with respect to the materials and any derivatives.)

With a shift from biological samples to digital samples, will the legal concept of national sovereignty over genetic resources be turned on its head? Will synbio facilitate a new wave of exclusive monopoly claims based on digital DNA sequences?

If the genetic pathways for produc-

*"Rather than send samples through the mail, sequences will be transferred electronically between researchers and directly into DNA synthesizers."*

– Rob Carlson<sup>225</sup>

*With a shift from biological samples to digital DNA samples, will the legal concept of national sovereignty over genetic resources be turned on its head?*

*Will synbio facilitate a new wave of exclusive monopoly claims based on digital DNA sequences?*

*The ability to synthesize genes will potentially lower barriers to patenting DNA sequences and the products that result.*

ing valuable natural substances that are traditionally derived from plants, animals and microorganisms can be identified by computers and fabricated by synthetic microbes in the laboratory, it could, among other things, usher in a new and more complex era of biopiracy.

Companies such as Amyris Biotechnologies foresee future profits from identifying new genetic pathways whether *in silico* or *in vivo*, re-creating them from scratch in microbes and then churning out products such as artemisinin, taxol or other plant-derived substances that were formerly sourced from indigenous and farming communities, or traditional healers. In theory, naturally-occurring chemical substances such as artemisinin are ineligible for patenting because they are regarded as “products of nature.” However, a 2004 report for the Department of Energy’s Biological and Environmental Research division notes that “the ability to synthesize genes will potentially lower barriers to patenting DNA sequences and the products that result by facilitating demonstration of utility and raising questions about the barrier of ‘product of nature’ doctrine.”<sup>229</sup>

In 2002, Syngenta (the world’s largest agrochemical corporation) filed a 323-page patent application related to its rice genome research that claimed monopoly control of key gene sequences that are vital for rice breeding and dozens of other plant species. The scope of the patent was unprecedented. Not only did the claims extend to at least 23 major food crops – they even extended to the use of gene sequences within computer readable sequencing information.<sup>230</sup> Civil society opposed

the patent and the application was eventually abandoned, but the monopoly claim illustrates the threat of far-reaching claims on digital DNA.

## **V. Synthetic Commodities – Implications for Trade**

*“We’re making it easier for people to make anything. They can make good things, they can make bad things, and if we’re going there, we’re going there very fast, at alarming exponential rates.”*

– Professor George Church, Harvard University geneticist and co-founder of Codon Devices<sup>231</sup>

Synthetic biologists are quick to identify the potential benefits of synthetic biology for the global South – particularly in the form of life-saving medicines and cheap bio-fuels. However, the most far-reaching impacts on poor economies, livelihoods and cultures are likely to come if synthetic organisms start to displace existing commodities:

**Once More with Feeling:** More than 15 years ago, ETC Group (then as RAFI) reported on US efforts to genetically engineer guayule – a desert shrub native to the southwestern US and Mexico – to increase yields of natural rubber.<sup>232</sup> In the same report, we highlighted USDA research on a fermentation system of microorganisms for large-scale production of high-quality rubber in a bioreactor. Just last year, we reported on academic and industry researchers’ attempts to replace rubber (or dramatically alter its properties) through nanoscale technologies. In both cases, we focused on the potential impacts on rubber growers and workers in the rubber-producing countries in the South, particularly Southeast Asia. While scientists have yet to master rubber production in

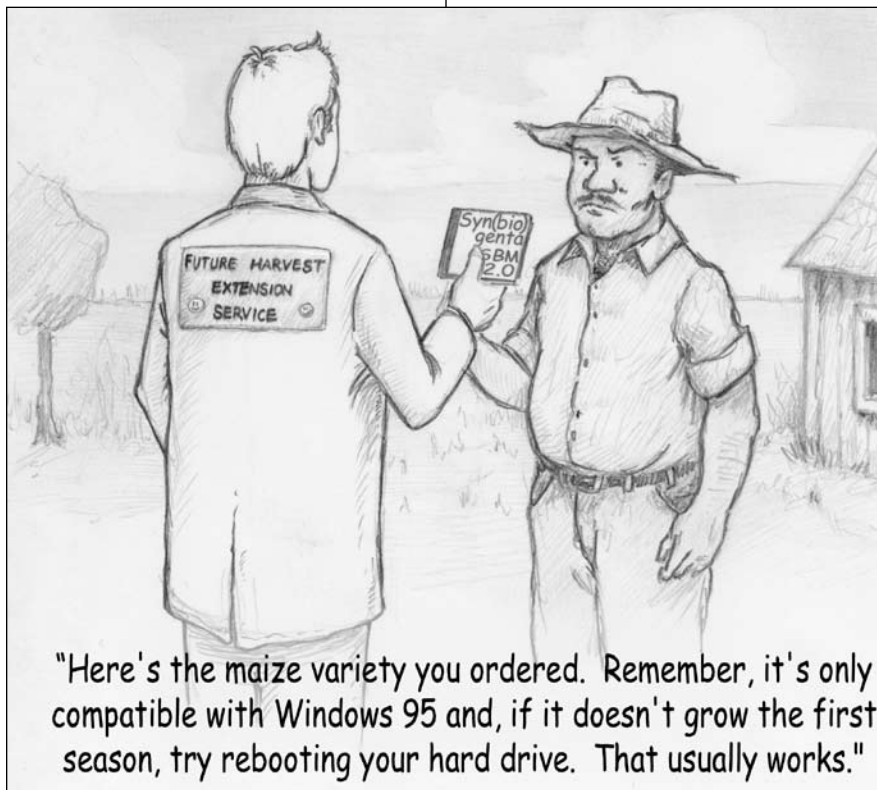
the lab, they haven't given up and now the project has bounced over to the field of synthetic biology.

Pathway engineers in Jay Keasling's lab are collaborating with the California-based Yulex Corporation and with researchers at the Colorado State Agricultural Experiment Station to engineer metabolic pathways in sunflowers and guayule that produce small quantities of natural rubber.<sup>233</sup> They are also attempting to engineer a rubber-producing tobacco. Alongside their engineering work on rubber crops, Keasling's colleagues intend to create a strain of bacteria that will produce high quality natural rubber straight from the microbe. They explain, "The goal of this proposed work is to produce, in microorganisms, rubber with the same qualities as natural rubber, and functionalized rubbers with novel properties that might be used for biomedical or other appli-

cations."<sup>234</sup> Initially they are transferring genetic networks for rubber production into three microbes (*Escherichia coli*, *Saccharomyces cerevisiae* and *Aspergillus nidulans*), and will ultimately focus on whichever organism works best as a productive host for their rubber biofactory. If rubber-producing synthetic organisms and enhanced rubber crops are commercially successful, the USDA hopes to meet all domestic rubber requirements this way. At present, the US accounts for one-fifth of global rubber consumption (around 1.2 million tonnes a year).<sup>235</sup> If successful, US-based rubber production would supplant over \$2 billion in export earnings from the South, likely depressing rubber prices and the livelihoods of small-scale rubber producers and plantation workers.

If the ability to cheaply produce other compounds from microbial factories – including drugs, tropi-

*The most far-reaching impacts on poor economies, livelihoods and cultures are likely to come if synthetic organisms start to displace existing commodities.*



*If the ability to cheaply produce other compounds from microbial factories – including drugs, tropical oils, nutrients and flavourings – is ultimately achieved through synthetic biology, there will be a dramatic impact on the global trade in traditional commodities.*

The question on everyone's mind will be "Is it safe?"

Like GMOs before them, organisms created through synthetic biology are far from being well understood.

cal oils, nutrients and flavourings – is ultimately achieved through synthetic biology, there will be a dramatic impact on the global trade in traditional commodities.<sup>236</sup>

## VI. Synbiosafety

*"Around the globe, people continue to worry that unnatural organisms containing recombinant DNA will become environmental headaches, if not pathogenic blights. For them, the news that scientists could soon genetically tinker more easily and more extensively is anything but good."* – Editorial in *Scientific American*, May 2006<sup>237</sup>

*"An engineer's approach to looking at a biological system is refreshing but it doesn't make it more predictable. The engineers can come and rewire this and that. But biological systems are not simple... And the engineers will find out that the bacteria are just laughing at them."* – Eckard Wimmer, molecular geneticist at the State University of New York at Stony Brook, who synthesised poliovirus<sup>238</sup>

Synbio's suite of extreme genetic engineering techniques comes in the wake of more basic genetically modified organisms that are not fully understood and have raised their own global biosafety concerns.<sup>239</sup>

While genetically engineered organisms are often evaluated under the principle of "substantial equivalence" – where the altered organism is equated with the organism's conventional, natural version based on genetic similarity – synthetic organisms cannot lay claim to substantial equivalence. The whole point of synthetic biology, after all, is to create novel organisms that are substantially different from those that exist in nature: synthetic DNA is

often made-to-order and extensively manipulated, it's not simply transferred from elsewhere in nature. As synbio products move from laptop to lab and out into the real world, the question on everyone's mind will be, "Is it safe?"

Synbio practitioners don't hesitate to offer up quotable quotes that acknowledge the possible pitfalls and unanswered questions related to creating synthetic organisms. In a recent *Scientific American* issue devoted to synthetic biology (June 2006), for example, the editors pointed out that one way to "kill this young science... is to underestimate the safety concerns."<sup>240</sup> But the question, ultimately, is how to address these concerns.

Synthetic biologists claim that because they are building whole systems rather than simply transferring genes, they can engineer safety into their technology (e.g., by programming cells to self-destruct if they begin reproducing too quickly). That assumes, of course, that the life builders have complete mastery over their art – an impossible standard since synthetic biologists, for all their talk of circuits, software and engineering, are dealing with the living wetware of evolution and all its unpredictability. Like GMOs before them, organisms created through synthetic biology are far from being well understood.

It's well worth reiterating a few lessons learned from the experience of genetic engineering:

**Living organisms evolve and mutate.** It's an oft-heard complaint from synthetic biologists that their creations don't like the *status quo*.

While the advantage of working with living cells is that they reproduce on their own, the downside is that they also evolve and mutate – changing the carefully crafted code that their makers have programmed into them. “From the perspective of an engineer, we have not yet learned how to design evolving machines that we can also understand,” admits Drew Endy, explaining, “No engineer has faced the puzzle of designing understandable evolving systems before.”<sup>241</sup> Ron Weiss, a synthetic biologist at Princeton University puts it more practically: “Replication is far from perfect... We’ve built circuits and seen them mutate in half the cells within five hours. The larger the circuit is, the faster it tends to mutate.”<sup>242</sup> Before asserting that synthetically engineered organisms are safe, synthetic biologists would need to show that they know how their creations will behave from generation to generation or indeed over hundreds of thousand of generations since microbial organisms reproduce quickly.

**There’s a lot we don’t know about living organisms.** Almost 55 years after the discovery of the double helix, molecular biologists are still uncovering new information about how genes work and what role they play in life functions. Only recently have scientists rejected conventional wisdom about genetic inheritance: no single gene exclusively governs the molecular processes that give rise to a particular inherited trait.<sup>243</sup> Scientists have moved away from the “one gene = one trait” assumptions of earlier days. Scientists are still learning that when they introduce a foreign gene into an organism it

can produce uncertainty about the gene’s function as well as the function of the DNA into which it is inserted.<sup>244</sup> They have also discovered that the vast “non-coding” sequences of DNA (so-called “junk” DNA), long considered irrelevant because they yield no proteins, may actually play indispensable roles in affecting an organism’s function, health and heredity.<sup>245</sup> Recent scholarship on gene regulation and expression emphasises the non-coding regions of DNA that transmit information in the form of RNA and on the importance of factors outside the DNA sequence.<sup>246</sup> For all the talk about synthetic bio’s genetic circuits and off-the-shelf parts, a living organism is not a logical and predictable “machine.”

**Living organisms can escape and interact with their environment.** In the future, *de novo* synthetic organisms may be built from multiple genetic elements that lack a clear genetic pedigree. According to Jonathan Tucker and Raymond Zilinskas, “the risks attending the accidental release of such as organism from the laboratory would be extremely difficult to assess in advance, including its possible spread into new ecological niches and the evolution of novel and potentially harmful characteristics.”<sup>247</sup>

Furthermore, several commercial projects are looking to manufacture and distribute compounds produced by synthetic organisms. Will substances produced by synthetic microbes behave identically to their known counterparts? In addition, proposals to use synthetic organisms for bioremediation or carbon sequestration imply the intentional

*Almost 55 years after the discovery of the double helix, molecular biologists are still uncovering new information about how genes work and what role they play in life functions.*

*For all the talk about synthetic bio’s genetic circuits and off-the-shelf parts, a living organism is not a logical and predictable “machine.”*



*Will substances produced by synthetic microbes behave identically to their known counterparts?*

environmental release of microorganisms with synthetic DNA.

Microbes, the main target of synthetic biologists, are promiscuous and can exchange genetic material with soil and gut bacteria.

The fashioning of short discrete synthetic pieces of code whether as 'BioBricks' or other active genetic elements raises concerns that syn-

thetic sections of DNA, under some circumstances, could be transferred to naturally occurring bacteria via the process of 'horizontal gene transfer.' Once incorporated into natural bacteria they could alter the functioning and behavior of natural microbial ecosystems – affecting the environment in unforeseen and unpredictable ways.

**Table 2: Companies with Synthetic Biology Activities**

<b>Company</b>	<b>Location</b>	<b>SynBio business area</b>	<b>Synthetic Biologists</b>
Ambrx www.ambrx.com	La Jolla, CA USA	Develops biopharmaceuticals utilizing artificial amino acids	Associated with Dr. Peter Schultz, Scripps Research Institute, San Diego, USA
Amyris Biotechnologies www.amyrisbiotech.com	Emeryville, CA USA	Developing synthetic microbes to produce pharmaceuticals, fine chemicals, nutraceuticals, vitamins, flavors and biofuels	Founded by Prof. Jay Keasling of University of California, Berkeley; CEO John G. Melo was previously president of U.S. Fuels Operations for British Petroleum; Vice President of Research is Dr. Jack D. Newman
Egea Biosciences www.egeabiosciences.com www.centocor.com	San Diego, CA USA	Now wholly owned by Johnson & Johnson. Develops innovative genes, proteins and biomaterials for J&J medical immunology subsidiary Centocor; Egea holds broad patent on genome synthesis	Founded by Dr. Glen Evans, formerly a leading investigator in the Human Genome Project
Codon Devices www.codondevices.com	Cambridge, MA, USA	Describes itself as a 'Bio Fab' able to design and construct engineered genetic devices for partners in medicine, biofuels, agriculture, materials and other application areas	Founders include: Prof. Drew Endy (MIT), Prof. George Church (Harvard), Prof. Jay Keasling (Berkeley), Prof. Ron Weiss (Princeton) and others
Diversa www.diversa.com	San Diego, CA USA	Diversa adds new codons to 'optimise' enzymes taken from natural bacteria to apply to industrial processes	Eric Mather, Vice-President of Scientific Affairs
DuPont www.dupont.com	Wilmington, Delaware USA	DuPont is partnering with Genencor, BP, Diversa and others to develop microbes that will produce fibers (Sorona) and biofuels	John Pierce is Vice President, DuPont Bio-Based Technology
EngeneOS www.engeneOS.com	Waltham, MA USA	Designs and builds programmable biomolecular devices from both natural and artificial building blocks	Founders include Prof. George Church (Harvard); Joseph Jacobson (MIT)
EraGen Biosciences www.eragen.com	Madison, WI USA	Develops genetic diagnostic technologies based on expanded genetic alphabet	Founded by Dr. Steven A. Benner
Firebird Biomolecular Sciences www.firebirdbio.com	Gainesville, FL USA	Supplies nucleic acid components, libraries, polymerases, and software to support synthetic biology	Founded by Dr. Steven A. Benner
Genencor www.genencor.com	Palo Alto, CA USA	Develops and sells biocatalysts and other biochemicals. Undertakes pathway engineering	Owned by Danisco
Genomatica www.genomatica.com	San Diego, CA USA	Designs software that models genetic network for synthetic biology applications	
LS9 www.LS9.com	San Francisco, CA, USA	Designs microbial factories that produce biofuels and other energy related compounds	Founders include Prof. George Church (Harvard)
Mascoma www.mascoma.com	Cambridge, MA, USA	Developing microbes to convert agricultural feedstock into cellulosic ethanol	Founded by Dr. Lee R. Lynd (Dartmouth College)
Protolife www.protolife.net	Venice, Italy	Developing artificial cells and synthetic living systems	Founded by Dr. Norman Packard
Sangamo Biosciences www.sangamo.com	Richmond, CA, USA	Produce engineered 'zinc finger' proteins for controlling gene regulation	
Synthetic Genomics www.syntheticgenomics.com	Rockville, MD USA	Developing minimal genome as chassis for energy applications	Founded by Dr. Craig Venter and Dr. Hamilton Smith; President is Dr. Ari Patrinos (formerly US Department of Energy)

## Synthetic Governance (Trust us. We're experts.)

*"There are two ways of dealing with dangerous technologies... One is to keep the technology secret. The other one is do it faster and better than everyone else. My view is that we have absolutely no choice but to do the latter."* – Tom Knight, *New Scientist*, 18 May 2006

If a small circle of synthetic biologists get their way, governance of extreme genetic engineering will be left entirely in their hands. Stephen Maurer is an attorney and director of the Information Technology and Homeland Security Project at Berkeley's Goldman School of Public Policy. In early 2006 he and two colleagues received funding from two foundations to investigate what level of oversight those working on synthetic biology deemed appropriate and palatable. Recognising that the field was already beginning to attract concern and criticism, particularly because of the potential to build new bioweapons, Maurer and his colleagues undertook 25 hour-long interviews and then prepared a white paper proposing a short list of soft, self-governance guidelines. The white paper's proposals were almost entirely focused on issues related to bioweapons. One proposal was for scientists working in the field of synthetic biology to boycott gene synthesis companies that did not screen orders for dangerous pathogens, and the development of software that could check genetic code for sequences that could be used maliciously. He also proposed a confidential hotline for synthetic biologists to check if their work, or the work of others, was ethically acceptable. These measures, put forward for formal adoption at the Synthetic Biology conference in

Berkeley in May 2006 (SynBio 2.0), would serve as pre-emptive action to avoid potentially more stringent government regulations. If the synthetic biologists could agree on these few proposals, the message to the rest of the world would be that the field is in responsible hands: Everything is under control. Trust us, we're experts.

The proposals carried echoes of an earlier episode in the history of gene technology. In 1975 scientists working with new recombinant DNA techniques (what we today call genetic engineering) met at Asilomar in Northern California amid growing calls for strong regulation of DNA technologies. The scientists agreed to impose a short-lived moratorium on some of their work, pending new biosafety frameworks. The Asilomar Declaration of 1975 is often portrayed as a shining example of responsibility and restraint by the scientific community, acting for the greater good of humanity. In reality, the Asilomar Declaration was a move by a handpicked group of elite scientists to preempt government oversight by promoting an agenda of self-regulation. Asilomar participants focused narrowly on biosafety issues – excluding broader social and ethical concerns. By appearing to voluntarily relinquish some recombinant DNA experiments (if only for a brief period of time), the Asilomar scientists took

*"If we choose to regulate the industry, we have to be willing to pay the price for that, which means there won't be cheap antimalarial drugs developed and there won't be potential biofuels developed and other drugs for other diseases and cleaning up the environment and all the things that come from this area."*

— Jay Keasling, *Discover*, December 2006

the heat out of a rising storm of debate, and avoided public participation on the issues.<sup>248</sup>

As early as October 2004, an editorial in *Nature* suggested there might be a need for an “Asilomar-type” conference on synthetic biology and reference to Asilomar has surfaced several times since within the community of synthetic biologists. Maurer’s consultation with synthetic biologists included two “town hall meetings,” one in Berkeley, CA and one in Boston, MA – home to the two largest academic communities of synthetic biologists in the US. Only a handful of people attended the Berkeley meeting while the MIT (Boston) meeting was slightly more energised, but still inconclusive. The chair of the Boston meeting, Drew Endy, noted candidly, “I don’t think [these proposals] will have a significant impact on the misuse of this technology.” In May 2006, all the leading science press were primed for “Asilomar 2.0” to take place in Berkeley at SynBio 2.0. *Nature* sent a reporter to blog live from the event while *Scientific American* put synthetic biology as their cover story and one of the original organisers of Asilomar, Professor David Baltimore, gave the keynote speech.

No civil society representatives were in attendance – those who tried to register were turned away due to “limited space.” In response to the synthetic biologists’ scheme for self-governance, a coalition of 38 civil society organizations, including ETC Group, drafted an open letter to conference attendees.<sup>249</sup> The letter dismissed the self-governance proposals as inadequate and sounded the alarm on synthetic biology to the international sci-

ence media. “Scientists creating new life-forms cannot be allowed to act as judge and jury,” explained Sue Mayer, director of GeneWatch. “The implications are too serious to be left to well-meaning but self-interested scientists. Public debate and policing is needed.” Those signing the open letter included social justice advocates (e.g., Third World Network), environmental groups (such as Greenpeace International and Friends of the Earth), farm groups (such as the Canadian National Farmers Union), bioweapons watchdogs (such as The Sunshine Project), trade unions (e.g., the International Union of Food Workers) and science organisations, including the International Network of Engineers and Scientists for Global Responsibility.

In the end, Asilomar 2.0 never quite took off. Inside the conference, too, self-governance proposals were coming under fire – though for different reasons. *New Scientist* noted that the proposal to boycott non-compliant gene synthesis companies was weakened because delegates didn’t want to hobble the gene synthesis industry. A final declaration emerged several weeks later, which didn’t rule out self-governance but placed it as one among a suite of possible governance approaches to synthetic biology: “We support ongoing and future discussions with all stakeholders for the purpose of developing and analyzing inclusive governance options, including self governance, that can be considered by policymakers and others such that the development and application of biological technology remains overwhelmingly constructive.”<sup>250</sup>

Proposals for self-governance of

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*If a small circle of synthetic biologists get their way, governance of extreme genetic engineering will be left entirely in their hands.*

synthetic biology also feature prominently in a December 2006 draft report “Synthetic Genomics: Options for Governance,” prepared by individuals from the J. Craig Venter Institute, Center for Strategic and International Studies (Washington, DC) and MIT. The 18-month study, funded by a \$570,000 grant from the Alfred P. Sloan Foundation, is limited in scope to the issues of biosecurity (i.e., bioweapons and bioterrorism) and biosafety (i.e., worker safety and the environment), fails to include consultation with civil society and focuses primarily on the US context for governance. One of the study’s primary criteria for effective governance is minimizing costs and burdens to industry and government. Rather than call for legally-binding regulations, the draft report emphasises a softer path such as options for monitoring and controlling gene synthesis firms and DNA synthesisers, educating practitioners and beefing-up Institutional Biosafety Committees (IBCs). IBCs in academic and commercial institutions, established by the US government’s National Institutes of Health guidelines, assess the biosafety and environmental risks of proposed rDNA experiments, and decide on the appropriate level of containment. Critics charge that IBCs are ineffective and unenforced.<sup>251</sup>

As yet, synthetic biology is not on the radar of any international treaties, agreements or conventions, although there are moves afoot to bring the matter for discussion at the Biological and Toxin Weapons Convention (BWC), which already bans the development, production, stockpiling and transfer of “microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes.”<sup>252</sup> Thus, the BWC already prohibits the synthesis of known or novel microorganisms for hostile purposes. Moreover, if synthetic organisms were designed to produce toxins, their development and production would theoretically be prohibited by both the BWC and the 1993 Chemical Weapons Convention. In 2005, the US National Institutes of Health established a Synthetic Biology Working Group affiliated with the National Science Advisory Board for Biosecurity to make proposals related to bioweapons. (See Box 4). Although it was reported in mid-2006 that the Office of the Director of National Intelligence in the US would form an advisory group to examine classified research in the area of synthetic biology, there is no further information available on the formation of this advisory body.<sup>253</sup>

## Recommendations

*“The discoverer of an art is not the best judge of the good or harm which will accrue to those who practice it.” – Plato, Phaedrus*

**Synbio without Borders:** The tools for DNA synthesis technologies are not only advancing at break-neck pace, they are becoming cheaper, geographically disperse and widely accessible. The economic and technical barriers to synthetic genomics research are collapsing:

- In 2000 the price of synthetic DNA was about \$10 per DNA base-pair; today it's less than \$1 per base-pair and by the end of 2007 the price could fall to 50 cents.
- The costs of equipping a lab for synthetic biology research are “low and dropping” and the skill-level required can be mastered by first-year university students with no training in biological sciences.<sup>254</sup>
- Within 2-5 years it may be possible to synthesise any virus; in 5-10 years it will become fairly routine to synthesise simple bacterial genomes.
- Around 66 commercial firms (with locations on five continents) specialise in synthesizing gene-and genome-length pieces of double-stranded DNA.
- Over 10,000 labs worldwide have the technical capacity to conduct synthetic biology research.<sup>255</sup>

Using desk-top DNA synthesisers or mail-order DNA from commercial gene foundries on the Internet, the do-it-yourself assembly of synthetic genes and genomes is possible almost anywhere in the world. According to Roger Brent, Director of the Molecular Sciences Institute in

Berkeley, California, “Novel DNA sequences are now designed and built *de novo* for introduction into living cells or incorporation into new organisms by undergraduate students in technical universities.”<sup>256</sup>

**Not “business as usual:”** ETC Group notes that some synthetic biologists are beginning to shun the spotlight and may seek to avoid public scrutiny by asserting that it is impossible to clearly distinguish their work from earlier advances in recombinant DNA technology (genetic engineering). Because synbio is all part of the same toolbox, they argue, it simply isn't possible to compartmentalise their research for purposes of regulatory oversight. This refrain (“synthetic biology is really nothing new”) is likely to be heard often in the coming months and years.

In reality, the ability to design and construct synthetic organisms from off-the-shelf DNA has the potential to revolutionise biology and amplify the power of technologies converging at the nanoscale. Synthetic biology is a nanoscale technology, and it must be considered in the broader context of converging technologies. Ongoing international dialogues on nanotechnology should incorporate synthetic biology in their discussions.<sup>257</sup>

**Beyond Regulation?** Given the widespread availability of synthetic biology tools, some argue that it will be impossible to regulate, and that efforts to control it will force research offshore or drive it underground. Governments cannot abdi-

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*Debate must go beyond biosecurity and biosafety to incorporate discussions about control and ownership of the technology and whether it is socially acceptable or desirable.*

*It is not for scientists to either control public discourse or determine regulatory frameworks.*

cate oversight of synbio because of the regulatory challenges it poses. Governments must determine what is safe and acceptable for society, encourage public dialogue and greater awareness of potential risks. As a starting place, ETC Group offers the following recommendations:

**There must be a broad societal debate on synthetic biology's wider socio-economic and ethical implications, including potential impacts on health, environment, human rights and security.** Debate must go beyond biosecurity and biosafety to incorporate discussions about control and ownership of the technology and whether it is socially acceptable or desirable. Because synthetic biology is highly de-centralised and its impacts will be global, governance options must be debated in an international framework.

**It is not for scientists to either control public discourse or determine regulatory frameworks.** In May 2006 civil society organizations rejected proposals put forth by a small group of synthetic biologists for voluntary, self-regulation of their work. In an open letter, 38 civil society organizations called on synthetic biologists to participate in a process of open and democratic oversight of the technology. Although some scientists and companies appear to be in favor of dialogue, that process has not begun.

**Civil society should meet at national, regional and international levels to evaluate and plan a coordinated response to the emergence of synthetic biology in the context of wider, converging technologies.** These meetings should be informed by, but not limited to, civil society

organizations and social movements such as farmers' organizations, trade unions, human rights advocates, peace, disarmament and environmental organizations.

**Whether by deliberate misuse or as a result of unintended consequences, synthetic biology will introduce new and potentially catastrophic societal risks.** ETC Group yields to the expertise of groups such as the Sunshine Project and the Center for Non-Proliferation Studies in making detailed recommendations on the biosecurity aspects of synthetic biology. However, in keeping with the Precautionary Principle, synthetic microbes should be treated as dangerous until proven harmless. At a minimum, environmental release of *de novo* synthetic organisms should be prohibited until wide societal debate and strong governance are in place, and until health, environmental and socio-economic implications are thoroughly considered. Governments should maintain zero tolerance for biowarfare agents, synthesised or otherwise, and adopt strong legal measures and enforcement to prevent the synthesis of biowarfare agents. Civil society must challenge the notion of 'defensive' bioweapons research because the line between 'defensive' and 'offensive' research is indistinguishable.

**International bodies must urgently review the implications of DNA synthesis and synthetic biology for their mandates.** In the future, the construction of synthetic genes or microbial genomes using commercially-available gene sequences will become faster and easier than obtaining biological samples from source countries, or from gene

banks. The United Nations Food and Agriculture Organization's Commission on Genetic Resources for Food and Agriculture should examine the potential implications of synthetic biology for *in situ* and *ex situ* genetic resource conservation and for Farmers' Rights. The UN Convention on Biological Diversity and its Subsidiary Body on Science, Technology and Technological Advice (SBSTTA) must also examine the potential implications of synbio for the protection of biodiversity and for existing rules on access to and exchange of genetic materials.

**The building blocks of life must not be privatised:** Despite earnest calls for "open source biology," exclusive monopoly patents are now being won on the smallest parts of life – on gene fragments, codons and even the molecules that make living organisms (i.e., novel amino acids and novel base pairs). Broad patents on synbio could be used to consolidate corporate power over a new generation of biological engineering and the parts, devices and systems for synthetic life.

Biosynthesis of high-value products (such as rubber and other South

commodities) has proven elusive in years past. Will synthetic biology succeed in engineering synthetic microbes to produce natural substances? If "genes now have the potential to be the design components of the future world economy,"<sup>258</sup> the UN Conference on Trade and Development should monitor the potential impacts on commodities, trade and people whose livelihood depends on the production and processing of raw materials.

**To facilitate coordinated global action, an international body should be established to monitor and assess societal impacts of emerging technologies, including synthetic biology.** Rather than approach technology assessment in a piece-meal fashion, governments and civil society should consider longer-term and ongoing strategies to address the introduction of significant new technologies. To break free from the cycles of crisis that accompany each new technology introduction, the international community needs an independent body that is dedicated to assessing major new technologies and providing an early warning/early listening system.

*Broad patents on synbio could be used to consolidate corporate power over a new generation of biological engineering and the parts, devices and systems for synthetic life.*

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## Case Study: Synthetic Biology's Poster Child – Microbial Production of Artemisinin to Treat Malaria

*The promise of unlimited supplies of a drug to treat malaria has become the raison d'être for synthetic biology.*

*Keasling's bacterial factories are already churning out copious amounts of priceless PR for the fledgling synbio industry.*

Over 90% of malaria deaths occur in sub-Saharan Africa. Global health initiatives have failed to deliver on simple prevention measures such as mosquito netting, and the worsening crisis has led the World Health Organization (WHO) to reverse a 30-year policy – it now backs the use of a 20<sup>th</sup>-century silver bullet, the controversial pesticide DDT, as a malaria prevention strategy. WHO regards artemisinin-based drugs as the best hope for treating over one million people – most of them African children – who would otherwise die of malaria each year. However, a global shortfall in the supply of natural artemisinin, which is extracted from sweet wormwood plants (*Artemisia annua*), has kept the price of this much-prized compound out of reach for poor people. Using synthetic biology to combat malaria is compelling: a technological fix comes to the rescue when investments in malaria prevention and control in Africa are declining, and failing.

In April 2006, Professor Jay Keasling of the University of California-Berkeley and 14 collaborators announced in *Nature* they had succeeded in engineering a yeast strain to produce artemisinic acid, which is a necessary step in the production of artemisinin itself.<sup>259</sup> Using sophisticated bioinformatics and screening techniques, the team claims to have discovered the genes involved in *Artemisia annua*'s natural production of artemisinic acid,

and managed to insert and express them in a modified yeast strain. The microbe thus behaves like a miniature factory to produce artemisinic acid. According to Keasling, what's left to do is to increase the yields of artemisinic acid, and then use "high-yielding chemistry" to convert artemisinic acid to artemisinin.

The promise of unlimited supplies of a drug that can roll back a global killer has become the *raison d'être* for synthetic biology and given the field a philanthropic sheen – reminiscent of biotech's much-heralded genetically engineered, Vitamin-A rich "Golden Rice" to feed the poor. (Since 2000, the biotech industry has used the promise of Golden Rice in public relations campaigns designed to win moral legitimacy for its genetically engineered crops – but the controversial product is not yet available.) Though they've produced only tiny quantities of artemisinic acid so far, Jay Keasling's bacterial factories are already churning out copious amounts of priceless PR for the fledgling synbio industry. The December 2006 issue of *Discover* names the Berkeley professor its first-ever Scientist of the Year and the magazine's editors ooze with admiration: "Through his significant synthetic biology advancements, Keasling is changing the world, making it a better place with every new discovery he makes."<sup>260</sup> But will betting on synthetic biology's medicinal microbes to tackle malaria (backed by \$42.5 million from the Bill and

Melinda Gates Foundation) divert attention and resources from other approaches that are less front page-friendly, but nonetheless sustainable and de-centralised? Will promising options for addressing malaria be cast aside in single-minded pursuit of synbio's silver bullet?

**The current situation:** WHO requires that artemisinin be mixed with other malaria drugs (a drug combination known as Artemisinin Combination Therapies or ACTs) to prevent the malaria parasite from developing resistance. Novartis's proprietary ACT drug (known as Coartem) is the only one that has received pre-clearance from WHO (meaning that it is approved for procurement by UN agencies), giving Novartis a virtual monopoly on ACT drugs. According to a 2006 study on artemisia conducted by the Royal Tropical Institute of the Netherlands: "This monopoly-like situation has created an imperfect market defined by scarcity of raw materials, speculation and extremely high retail prices."<sup>261</sup>

Under contract to WHO, Novartis provides Coartem at cost (US\$ 0.90 to treat infants; US\$ 2.40 to treat adults) to the public sector in malaria-endemic countries in the South. A two-tier pricing system allows Novartis to sell their ACT compound for ten times the cost to Northern markets and international travelers. Other drug companies are developing ACT drugs, with Sanofi-Aventis closest to having a marketable product.<sup>262</sup>

Novartis currently buys almost all of the world's wormwood crop, sourcing from thousands of small farmers across China, Vietnam,

Kenya, Tanzania, India, Uganda, Gambia, Ghana, Senegal and Brazil. In East Africa, an estimated 1,000 small-scale farmers (average 0.3 hectares) and 100 larger scale farmers (average 3 hectares) currently grow artemisia.<sup>263</sup> In light of global demand and recent campaigns to reinvigorate the fight against malaria, that figure is expected to grow to approximately 5000 smallholders and 500 larger-scale farmers.<sup>264</sup>

The report by the Royal Tropical Institute of the Netherlands concludes that the current artemisia shortfall could be met solely by increasing cultivation of wormwood, especially in Africa. Increasing local production is attractive as a sustainable and decentralised approach. "From a technical point of view, it is possible to cultivate sufficient artemisia and to extract sufficient artemisinin from it to cure all the malaria patients in the world. An ACT could be made available at an affordable price within just 2-3 years."<sup>265</sup> The report estimates that between 17,000-27,000 hectares of *Artemisia annua* would be required to satisfy global demand for ACT, which could be grown by farmers in suitable areas of the South.<sup>266</sup>

The Institute's report warns, however, that the prospect of synthetic artemisinin production could destabilise a very young market for natural artemisia, undermining the security of farmers just beginning to plant it for the first time: "Growing Artemisia plants is risky and will not be profitable for long because of the synthetic production that is expected to begin in the near future."<sup>267</sup>

**Sold on synbio's synthetic vision:** Keasling's team believes that using

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*Will promising options for addressing malaria be cast aside in single-minded pursuit of synbio's silver bullet?*

*Are local production, extraction and even manufacturing of ACTs possible in regions where malaria is prevalent?*

synthetic microbes to manufacture artemisinin could increase supplies more quickly and reliably than planting new crops. "You would need to plant the state of Rhode Island to meet demand," quips Jack Newman, co-founder – along with Keasling – of Amyris Biotechnologies, the company that will bring synthetic artemisinin to market.<sup>268</sup> Amyris predicts that microbial production will lower the cost of artemisinin to 25 cents per dose.<sup>269</sup> The company's non-profit partner, OneWorld Health, will steer the product through the regulatory process and conduct preclinical studies to determine the safest artemisinin derivatives.<sup>270</sup>

However, large-scale production of synthetic artemisinin still faces significant technical difficulties. OneWorld Health explains that "the yield of artemisinic acid would need to be improved several hundred fold to be economically acceptable for large-scale manufacturing."<sup>271</sup> Meanwhile, WHO notes that "clinical trials have not yet begun, and filing for regulatory approval will probably not occur before 2009 to 2010."<sup>272</sup> Keasling, too, sees late 2009 or early 2010 as the earliest realistic target for mass distribution.<sup>273</sup>

If microbial production of synthetic artemisinin is commercially successful, pharma giants like Novartis would benefit because it will allow them to replace a diverse set of small suppliers with one or two conveniently located production factories. The Royal Tropical Institute notes that, "pharmaceutical companies will accumulate control and power over the production process; artemisia producers will lose a source of income; and local produc-

tion, extraction and (possibly) manufacturing of ACT in regions where malaria is prevalent will shift to the main production sites of Western pharmaceutical companies."<sup>274</sup>

**Could artemisia be a viable crop for small farmers in sub-Saharan Africa?** Are local production, extraction and even manufacturing of ACTs possible in regions where malaria is prevalent? The Dutch researchers who studied this possibility conclude that it won't be easy – requiring not only a hefty capital investment, but also "a total redesign of the supply and distribution chain."<sup>275</sup> They suggest a number of policies that could be implemented to promote cultivation of *Artemisia annua* while at the same time protecting farmers from un-due risk. For example, a procurement fund could be established in Africa to stabilise the market for artemisia; quality seed could be made available to African farmers; other medicinal crops could be promoted to reduce the economic risk to farmers; a task force could be established to enhance transparency, coherent policy making and knowledge sharing.<sup>276</sup>

Where ACT drugs are not accessible or affordable, community-based efforts are focusing on local production of artemisia plants for use in herbal tea to treat malaria. Conventional health systems such as WHO do not sanction the use of artemisia tea because of the difficulty of establishing a standard dosage and quality control. However, Anamed (Action for Natural Medicine), a Christian-based group of scientists and health workers, believes that the tea is effective in treating upwards of 80 percent of malaria cases.<sup>277</sup> Anamed's 'grow your own'

approach to fighting malaria provides artemisia seeds, community workshops and agronomic support for small-scale plots based on mixed farming methods across Asia and Africa. Anamed promotes a method of combining the tea with other compounds (either cheap medicines or locally adapted herbs) to mimic the combination effect of pharmaceutical ACTs, but without using proprietary drugs. Anamed believes that compounds found in artemisia leaves, including 36 different flavonoids, enhance the anti-malarial properties of the tea (which they say are lost when the compound is purified for drug use).<sup>278</sup>

While the use of artemisia tea may be controversial, the need to increase the world's supply of artemisia is not. Anamed has developed a variety of artemisia adapted to African conditions known as *Artemisia*

*annua anamed* (A-3) and the group has introduced over 715 artemisia growing projects in 75 countries.<sup>279</sup> Their partners include the World Agroforestry Center (ICRAF) in Mozambique, which has taught thousands of southern African farmers in their network how to grow artemisia from stem cuttings.<sup>280</sup> Anamed's seeds are sold for \$.01 per seed and each plant can treat up to eight malaria sufferers. Those plants can then be further propagated by taking stem cuttings.<sup>281</sup>

No one knows if synthetic biology will ultimately deliver safe and sufficient quantities of low-cost artemisinin for controlling malaria in the developing world. The Gates Foundation should insure that its focus on a synbio anti-malarial drug does not foreclose options for community-based, farmer-led approaches.

***No one knows if synthetic biology will ultimately deliver safe and sufficient quantities of low-cost artemisinin for controlling malaria in the developing world.***

## Glossary

**Amino Acid** – Small molecules that link together to form proteins; often referred to as “the building blocks” of proteins. 20 unique amino acids have been identified.

**Biopiracy** – The appropriation of the knowledge and genetic resources of farming and indigenous communities by individuals or institutions who seek exclusive monopoly control (patents or intellectual property) over these resources and knowledge. ETC group believes that intellectual property is predatory on the rights and knowledge of farming communities and indigenous peoples.

**Chromosome** – A long, continuous piece of DNA that contains many genes, regulatory elements and other intervening nucleotide sequences.

**Codon** – A series of three chemical bases linked together in a specific order. During protein synthesis, it is the order of the codon that determines which amino acid will be added to the protein under construction within the cell. Each codon carries the code for a specific amino acid.

**DNA** – A self-assembling, cellular molecule that contains the genetic instructions for the development and function of living things. DNA is made up of simple units called nucleotides that are held together by a “backbone” made of sugar and phosphate groups. DNA’s structure is a double helix.

**Isoprenoid** – a diverse class of chemical molecules produced primarily by plants. Although over 50,000 isoprenoids are known, only a small fraction have been exploited for pharmaceutical and industrial purposes. Taxol (derived from the yew tree) and artemisinin (derived from the wormwood tree) are examples of isoprenoids.

**Nucleotide** – One of the structural components of DNA and RNA. A nucleotide consists of a base (one of four chemicals: adenine [A], thymine [T], guanine [G], and cytosine [C]) plus a molecule of sugar and one of phosphoric acid.

**Oligonucleotide** – Short, single-stranded sequences of DNA, typically made up of twenty or fewer bases (though automated gene synthesizers produce oligonucleotides that may be 200 bases long).

**Synthetic Biology** (also known as Synbio, Synthetic Genomics, Constructive Biology or Systems Biology) – The design and construction of new biological parts, devices and systems that do not exist in the natural world and also the redesign of existing biological systems to perform specific tasks. Advances in nanoscale technologies – manipulation of matter at the level of atoms and molecules – are contributing to advances in synthetic biology.

Sources: ETC Group, Genetics Home Reference Glossary (<http://ghr.nlm.nih.gov/ghr/glossary/aminoacid>), Wikipedia ([www.wikipedia.org](http://www.wikipedia.org)), Amyris Biotechnologies, Inc.

## Endnotes

On December 13, 2006, all of the ULs provided in the endnotes were active.

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