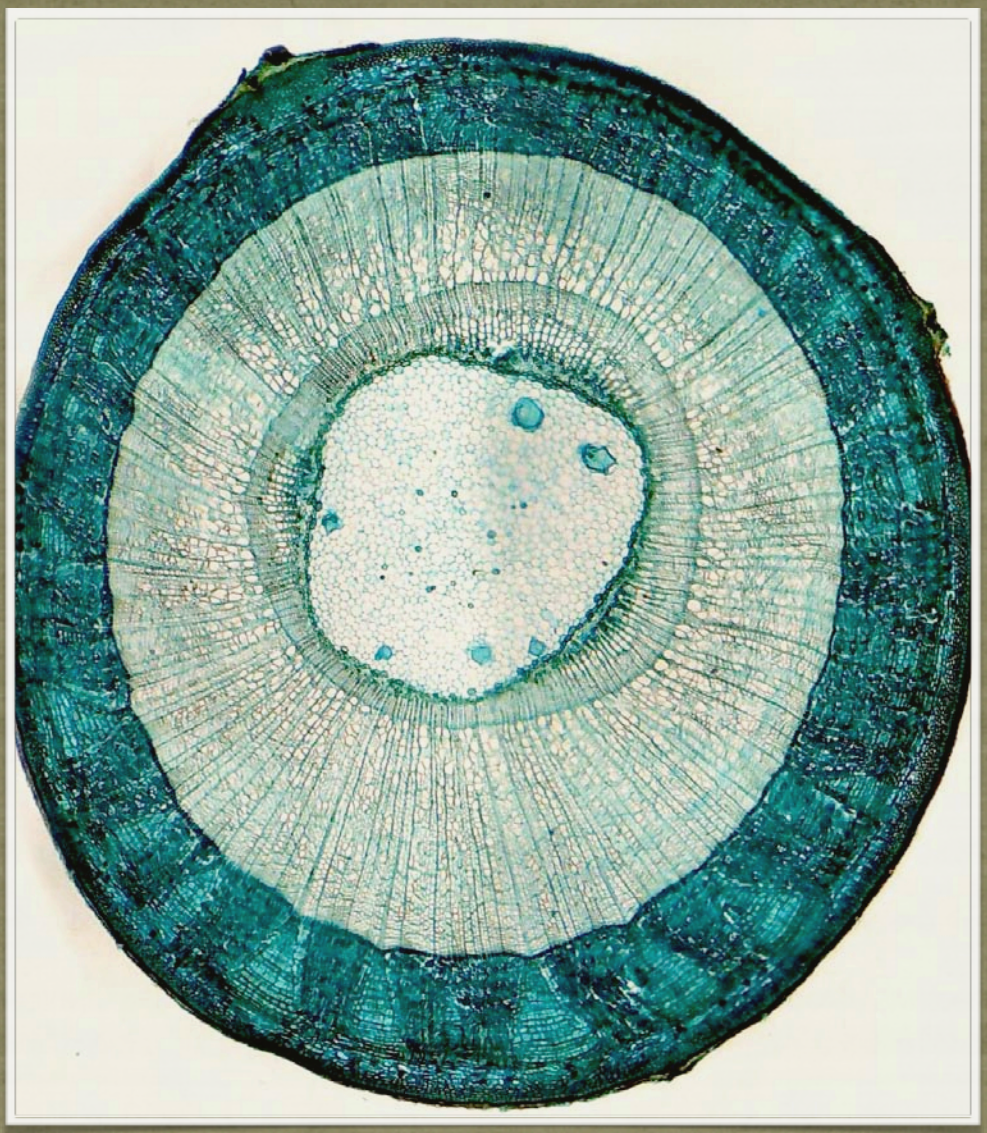

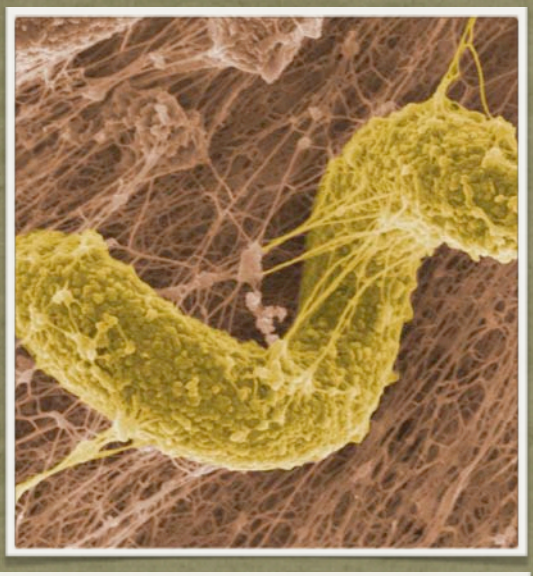

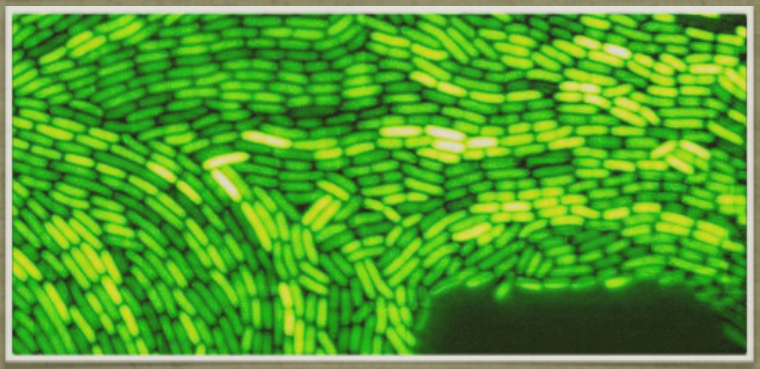

SYNTHETIC BIOLOGY NEWSLETTER

An LIS Consult and Synthetic Biology Project Initiative

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The Synthetic Biology Newsletter is an initiative of LIS Consult and the Synthetic Biology Project of the Woodrow Wilson International Center for Scholars. The newsletter is financially supported by the Commission on Genetic Modification and the Rathenau Institute, both in the Netherlands.

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COMMISSIE COGEM GENETISCHE MODIFICATIE

Synthetic BIOLOGY PROJECT

In this issue

I. Synthetic biology and the bio-based economy

The production of next generation biofuels is one of the major targets for commercial application of synthetic biology. Energy production is a field of application that has considerable public support. And it is about to become big business.

In 2007 British Petroleum selected the University of California, Berkeley to lead the Energy Biosciences Institute. It is a $500 million energy research consortium with partners Lawrence Berkeley National Lab and the University of Illinois. A year ago, Craig Venter's company, Synthetic Genomics announced a $300 million deal with Exxon Mobil. The plan is to create fuel-producing algae, in part by using synthetic genes.

On May 27, in a hearing for the Health and Energy Committee on Energy and Commerce of the U.S. House of Representatives, Jay Keasling told how the Joint BioEnergy Institute (JBEI) is exploring the potential of synthetic biology to advance the development of next generation advanced "drop-in" fuels that perform better than ethanol.

From petroleum to sugar?

Keasling is also the founder of Amyris Biotechnologies Inc. This company is one of the key players that projects the global synthetic biology market to exceed $ 4.5 billion by the year 2015. Amyris is specialized in applying synthetic biology to provide alternatives to petroleum-sourced fuels and chemicals. A brief overview of Amyris's activities demonstrates that apart from biofuels, synthetic biology will be applied to pave the way for a bio-based economy.

The idea is to replace molecules that might otherwise be produced from petroleum, with sugarbased products. Amyris is not only applying a type of biological pathway engineering that still looks like a sophisticated mode of genetic engineering, it also builds on established interests in sugar cane production. The company demonstrates that commercial strategies are built on existing technologies and economic infrastructures.

Radical approach

Meanwhile, far more radical approaches of synthetic biology are being developed. Think of a new artificial photosynthetic material. It uses plant, bacterial, frog and fungal enzymes, by trapping them within a foam housing. Such artificial energy production platforms are more radical because they do not rely on plants or algae. They are not competing with food production, since they do not use soil. And they are far more efficient in capturing and converting energy from the sunlight since they do not have to maintain life and reproduce. But, these more radical applications may require fundamental transitions in the structure of energy production and distribution. That makes commercial incentives like the ones BP and ExxonMobil are involved in, less likely.

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Amyris Paves the Way for Sustainable Fuels and Chemical Production

Amyris Biotechnologies, Inc. will probably be the first company to bring applications of synthetic biology to the market. Founded in 2003, the company developed an industrial synthetic biology platform to provide a range of biobased products. What can we expect in the coming five years?

"Sugarcane" Photo courtesy of R Desai

Amyris is a renewable products company. It aims to shrink the world's carbon footprint. Using technology and synthetic biology to produce more environmentally friendly products, it wants to provide consumers with renewable chemicals and fuels.

Amyris recently started to scale up its production and distribution capacities. It entered into agreement with several petrochemical companies, and succeeds in raising considerable amounts of cash. (*see below) Since it's inception in 2003, Amyris has secured $244 million in private funding.

Brazilian sugarcane

On December 9, 2009 Amyris Brasil announced that it would be joining three Brazilian sugar and ethanol producers. The aim of this merger is to manufacture and distribute high quality and renewable fuels and chemicals from sugar cane molasses. As of December 3, 2009, Amyris also has a 40% stake in the Boa Vista mill. The plan is to use the mill as a production facility to create the renewable fuels and chemicals Amyris is planning to market in 2011.

The agreement between these four parties creates a company that produces entirely renewable products by combining technology, industrial-scale manufacturing and product distribution. The resulting products are meant to be "higher quality, renewable … [and] with lower capital intensity than petroleum-based products."

The production will likely begin with Amyris's current technology, which employs synthetic biology to change the metabolic pathways of microorganisms. This can change sugar into

one of the 50,000 possible molecules that can be used in energy, pharmaceutical and chemical production. This process has already been utilized to create the low cost anti-malarial drug, artemisinin. As its first product, Amyris wants to produce a renewable diesel fuel that can be used in low temperature diesel engines, and can be integrated into our existing infrastructure.

On June 22, 2010 Amyris and Cosan S.A. announced plans to establish a joint venture for the worldwide development, production and commercialization of renewable intermediate chemicals for specific industrial and automotive applications. Cosan is a fully-integrated company in the sugar, ethanol and energy sectors. With 62 million tons of crushing capacity, it is the largest mill group in Brazil. Cosan has established product development, manufacturing and marketing capabilities. Under the joint venture, the parties will jointly commercialize the target products throughout the world. The parties expect to complete a definitive agreement later this year.

Good news

The merger and the development of alternative sources of energy, hold great promise for future energy policy. And for societal use, of course, it is good news that by facilitating the transition from fossil fuels towards renewable sources of energy, petroleum-dependant countries will be able to regain some sovereignty in their energy consumption.

But there's a downer too. As with any large scale produce farm, sugar cane plantations contribute to environmental degradation. Think of burning cane before harvesting, using minimal yet some pesticide and herbicide. What to think of deforestation? Or pushing other crop cultivation and cattle herding into Amazonia?

However, it is an undeniably environmentally and politically conscious step to alter present habits of energy production and consumption. So society on a global scale should reap the benefits. Whether this new technique of fuel production is also a mean to a more environmentally conscious end, or an end in itself; only time can tell.

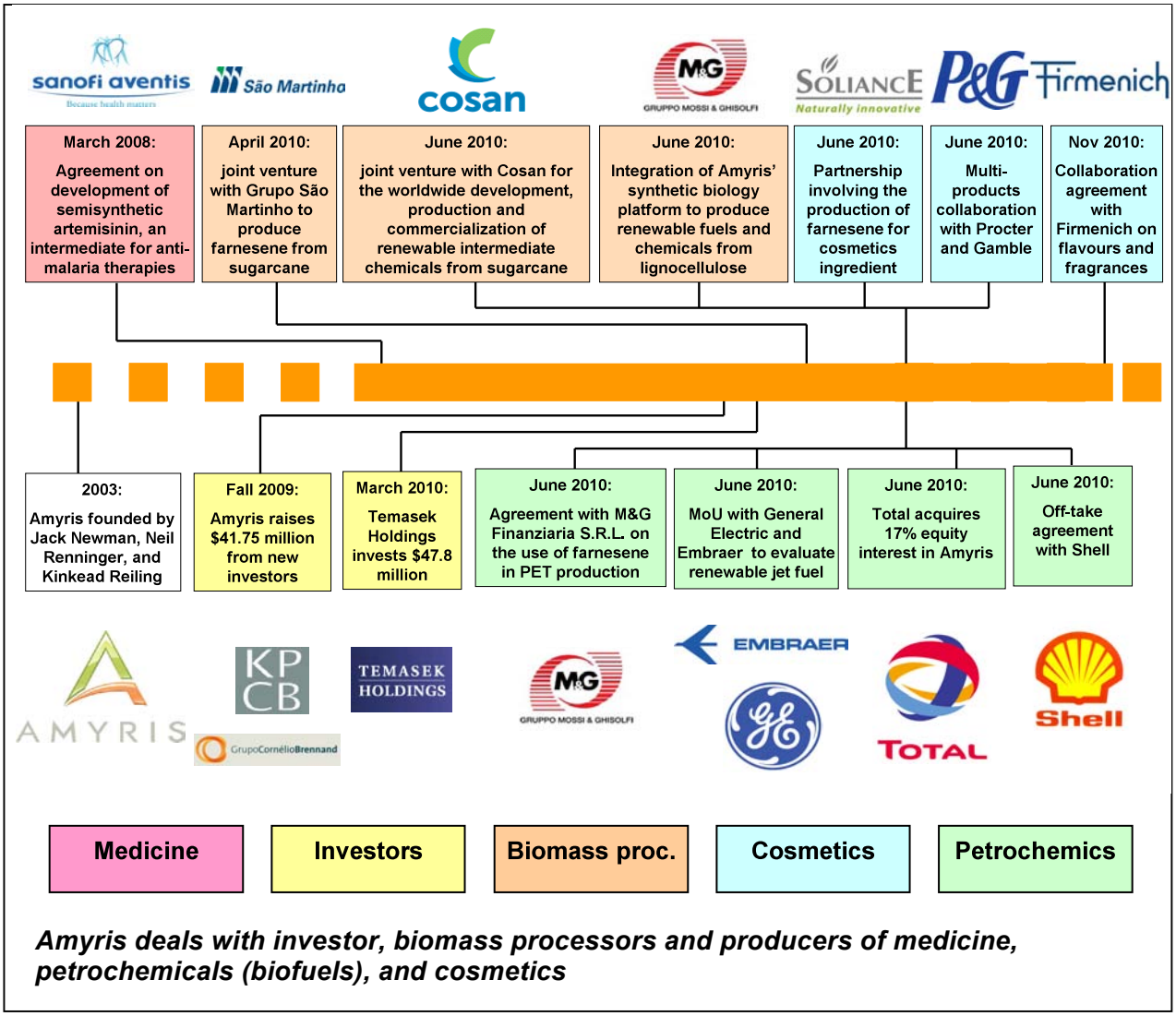
Amyris investors and alliances

In the fall of 2009 Amyris raised $41.75 million from new investors such as GrupoCornelioBrennand of Brasil and Naxos UK. It also raised new funds from previous investors including Khosla Ventures, Kleiner Perkins Caufield & Byers, TPG Biotech and Votorantim Novos Negocios. In March 2010, Temasek Holdings, an Asia investment house headquartered in Singapore, invested another $47.8 million. At the Initial Public Offering in September 2010 the company sold 5.3 million shares and collected almost $ 85 million.

In April 2010, Amyris announced a joint venture with Grupo São Martinho, one of the largest sugar and ethanol producers in Brasil, to produce Amyris renewable products. The joint venture was created to build the first facility located at Usina São Martinho in Pradópolis, São Paolo state. Usina São Martinho is one of the largest processors of sugarcane in the world, having milled 8.1 million tons of sugarcane during the 2009/2010 harvest season.

Amyris will provide genetically engineered yeast to produce farnesene. This is a molecule which could be an ingredient in a wide range of consumer and industrial products, including detergents, cosmetics, perfumes and industrial lubricants. Amyris has agreed that Grupo São Martinho may convert a second mill to produce Amyris products.

Farnesene, or Biofene™, is also produced by Soliance, using Amyris's biotech process in its industrial fermentation facilities. Amyris and Soliance have entered into a partnership in June 2010. They are combining Amyris's industrial synthetic biology platform with Soliance's leadership position in the production and commercialization of renewable cosmetic ingredients. Soliance will convert Biofene™ into squalane[1] which will be marketed directly by Soliance to cosmetics industry customers.



Amyris deals with investor, biomass processors and producers of medicine, petrochemicals (biofuels), and cosmetics

In the same month, Amyris entered into a series of agreements with The Procter & Gamble Company, a global leader in consumer products. Procter & Gamble also focuses on the use of farnesene (BiofeneTM) in 'certain specialty chemical applications' within its products. In connection with these collaboration agreements, the parties have also entered into a supply agreement for Biofene which 'would commence upon successful completion of certain technical and commercial milestones'.

[1] Squalane is used in cosmetics as an emollient and moisturizer. Squalane is a saturated form of squalene, a natural product sourced from shark liver or from vegetable sources such as olive oil. According to Amyris, shark hunting raises environmental and other concerns, and olive oil squalane is subject to availability issues and price variability due to its interrelationship with the consumption of the edible oil.

Amyris's farnesene will also be used as an ingredient in PET processing. On June 24, Amyris announced a collaboration agreement with M&G Finanziaria S.R.L. This is an Italian chemical engineering company that develops PET resins for container packaging and PET packaging films for the food market. The parties will also work together to combine access to low cost sugars by integrating M&G's ProEsa[2] lignocellulosic process with Amyris's synthetic biology platform to produce renewable fuels and chemicals.

In November 2010 the company entered into a collaboration and joint development agreement with Firmenich, the largest privately-owned fragrance and flavor company, based in Switzerland. Under the agreement, Firmenich will fund technical development at Amyris to produce a source of a key ingredient for the fragrance and flavor market. Amyris will manufacture and supply product to Firmenich, Firmenich will market and distribute the product, and the parties will share in the economic value derived. The agreement between the parties also grants worldwide exclusive commercialization rights in fragrance and flavor to Firmenich for the ingredient, which will be manufactured by Amyris. In addition, Firmenich has an option to collaborate with Amyris to develop a second ingredient.

Jet fuel, diesel and other chemicals

In November 2009 Embraer, General Electric, and Amyris signed a Memorandum of Understanding to evaluate the technical and sustainability aspects of Amyris's patented *No Compromise*® renewable jet fuel. *No Compromise*® is a mixture of limonene and farnesene.

The initiative could culminate in a demo flight by early 2012 of an Embraer E-Jet. The goal is to accelerate the introduction of a renewable jet fuel that could significantly lower greenhouse gas (GHG) emissions. It should be a long-term sustainable alternative to petroleum-derived jet fuel.

In June 2010 Amyris entered into an off-take agreement with Shell for the supply of *No Compromise*® diesel. The parties have agreed to the terms under which Shell may purchase the renewable fuel from Amyris, including pricing relative to a defined biodiesel price index.

The companies intend to cooperate to obtain the necessary European approvals for use of this fuel. According to Amyris, unlike biodiesel and ethanol, *No Compromise*® diesel is a hydrocarbon enabling it to blend with petroleum diesel at much higher levels than typical biofuels without losing performance. The U.S. Environmental Protection Agency has officially registered Amyris's renewable diesel fuel at a 20% blend rate.

At about the same time oil and gas company Total agreed to acquire approximately 17% equity interest in Amyris. Total will have the right to appoint a member of the Amyris Board of Directors. Total and Amyris R&D teams will work together to develop new products and build biological pathways to produce and commercialize renewable fuels and chemicals.

[2] The aim of ProEsa is to develop a complete crop-to-ethanol value chain through a conversion technology able to transform selected ligno-cellulosic material into bio-ethanol in a sustainable way. Currently, ProEsa is at the stage of a demonstration plant.

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Frogs, Foam and Fuel

Engineers from the University of Cincinnati have devised a super efficient synthetic system: a foam that captures energy and removes excess carbon dioxide from the air — thanks to semi-tropical frogs.

Illustration by Megan Baudendistel

In the last decade, governments have included the use of biomass for biofuel production as a serious option in their energy policies. However, biomass production and its conversion to bioethanol is a rather inefficient way of capturing and storing solar energy.

In natural photosynthesis, plants absorb solar energy and carbon dioxide and then convert it to oxygen and sugars such as glucose and fructose. These plant sugars can be converted to ethanol as a renewable energy source. Unfortunately, this process of solar energy conversion is not very efficient. Due to limitations in wavelength sensitivities and extensive cellular processes (including growth, repair, and maintenance), plants convert only 1-2% of usable energy into sugars. Moreover, the production of plant sugars requires that limited land and water resources be diverted, in part, to biomass production.

Artificial photosynthetic material

Now, thanks to a semi-tropical frog species, engineering researchers at the University of Cincinnati are finding ways to take energy from the sun and carbon from the air to create new forms of biofuels. To produce these sugars from sunlight and carbon dioxide, researchers developed a new artificial photosynthetic material which uses plant, bacterial, frog and fungal enzymes, by trapping them within a foam housing.

Frog Foam

Foam was chosen because it can effectively concentrate the reactants. But it also allows considerable light and air penetration. The design was based on the foam nests of a semi-tropical frog called the Tungara frog, which creates very long-lived foams for its developing tadpoles.

The researchers first divided the entire photosynthetic system into three independent reactions: 1) the conversion of energy from the sunlight (photons) to the natural energy molecule ATP[3], 2) a RuBisCo[4] carbon fixation assay, and 3) a glucose producing assay. After demonstrating the system as separate experiments, the three reactions were combined

[3] ATP provides the energy that drives the so-called Calvin cycle. The Calvin cycle makes sugars from carbon dioxide and NADH, another energy-rich product of photosynthesis.
[4] RuBisCo is the carbon-fixing enzyme ribulose- 1,5-biphosphate carboxylase/oxygenase.

and an assessment of the full process was conducted. The peak chemical conversion efficiency was 96% (as compared to the 1-2% of plants prior).

Advantages over plants and algae

The artificial system has several advantages over plants and algae. First of all, the system does not have to maintain life and reproduce, so it converts all captured energy to sugars. The foam also uses no soil, so food production will not be affected. In natural plant systems, excessive carbon dioxide shuts down photosynthesis. But the frog foam based system does not have this limitation due to the bacterial-based photo-capture strategy. Thus, the frog foam based syste can be used in highly enriched carbon dioxide environments, like the exhaust from coal-burning power plants. Finally, by designing the photosynthetic foam to synthesize sugar directly, biofuels like DMF (2,5-dimethylfuran) could be produced, which has advantages over ethanol because of its 40% higher energy density, higher boiling point and insolubility in water that makes it more suitable for pipeline transport.

Research groups from all over the world are working on similar systems based on photosynthesis. Recently, a consortium of Dutch research groups received a government grant of 25 million Euros to establish a Center for Photosynthesis. This Center will focus on three fields of research: 1) systems biology of photosynthesis processes, 2) re-engineering organisms for optimal photosynthetic energy conversion into biomass, and 3) energy-tapping before the energy is converted into biomass, resulting, for instance, in solar cells that yield methanol instead of electricity.

Making it work outside the lab?

Although the next step for the Cincinnati team will be to try to make the technology feasible for large-scale applications like carbon capture at coal-burning power plants, it is unclear whether and when this type of promising research will result in commercial application of new energy production methods. For this to occur, there has to be sufficient proof that the technology is working in large-scale production facilities and outside the lab. Perhaps even more important will be whether commercial incentives are developed for energy companies.

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II. Synthia's (not so) revolutionary character

The announcement of the first self-replicating synthetic bacterial cell by the J. Craig Venter Institute (JCVI) in May 2010 caught worldwide media coverage. 'This is not (yet) new life', the general comments read. Or, as Craig Venter put it himself: "It is not life from scratch."

Venter called the work "a baby step" in the field of synthetic biology. But ultimately, as he explained to the Health and Energy Committee on Energy and Commerce in the US House of Representatives, "Synthetic genomics is different [from standard molecular biology/genetic engineering] in that scientists start with digital information in the computer, which allows for the design of entire synthetic chromosomes to replace existing chromosomes in cells."

Disruptive character

The question of 'newness' and the revolutionary or even disruptive character of synthetic biology is not only a purely scientific issue. It is highly relevant for society, and has strategic dimensions. For instance: the answer to the question of newness is decisive for decisions on research and regulatory policies. On the one hand, scientists and research institutes will tend to define synthetic biology as 'new' when they want to attract new investments. On the other hand, really new approaches in biology will trigger policy makers to call for stricter or new regulation. Moreover, the question whether 'new life forms' can be created or not, will influence public perception and acceptance.

Philosophical watershed?

A comment in the Vatican's official newspaper (L'Osservatore Romano) on the self-replicating synthetic bacterium, stated that "It is not the creation of life, but the replacement of one of its motors". It is illustrative for the majority of the institutional comments that JCVI's achievement is not a philosophical watershed. In a public panel discussion about synthetic biology organised by the German Ethics Council, some of the participants likewise called for a "de-dramaticising" of the issue. On the other hand, President Obama asked his bioethics commission to study the implications of the JCVI research in a broad sense, suggesting that synthetic biology may raise new issues. This commission is expected to make recommendations on "any actions the Federal government should take to ensure that America reaps the benefits of this developing field of science while identifying appropriate ethical boundaries and minimizing identified risks" before the end of the year.

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III. Society's response

Government funding for synthetic biology is on the rise, but the way in which society responds to new technologies is an important factor in their success or failure. With synthetic biology, so far, civil society organizations (CSOs) seem to build on their 1980's genetic engineering strategy: they focus on the risks of synthetic biology, and call for a moratorium and stricter regulation. Scientists and public policy authorities seem to have learned their GMO lessons. There is an increased awareness of the importance of public engagement in potentially controversial technological developments.

A new and first-of-its-kind analysis by the US Woodrow Wilson Center found that the U.S. government has spent around $430 million on research related to synthetic biology since 2005, with the Department of Energy funding a majority of the research. By comparison, the analysis indicated that the European Union and three individual European countries – the Netherlands, United Kingdom, and Germany – had spent approximately $160 million during that same period. Estimates have placed the current annual synthetic biology research market at $600 million, a sum that has the potential to exceed $3.5 billion over the next decade. The list of potential applications in energy, environment, health and other areas is long and growing. Along with its potential benefits, there are also concerns about the ethical, legal and social implications of synthetic biology. In response to these concerns, approximately 4 percent of the U.S. funding and 2 percent of the European funding is being spent for so-called ELSI research.

CSO testimony

Synthetic biology is also increasingly grasping attention from CSOs. In a hearing by the U.S. House of Representatives Energy and Commerce Committee, Friends of the Earth, the ETC Group and the International Center for Technology Assessment sent a testimony to the committee's chairman, calling on the Congress to implement a moratorium on the release of synthetic organisms into the environment and also their use in commercial settings. This moratorium should remain in place until there is an adequate scientific basis on which to justify such activities, and until due consideration of the associated risks for the environment, biodiversity, and human health, and all associated socio-economic repercussions, are fully and transparently considered. Testbiotech, a German CSO concerned with the ecological, social and ethical aspects of biotechnology, has launched an initiative with more or less the same demands.

Public dialogue

Besides CSO's responses and activities, there are strong calls for more effective public engagement, without which "there will be no synthetic biology in Europe" according to Colin Macilwain in a column in Nature of June 16th, 2010. This lesson, learnt from the European debate on genetically modified crops, is at the heart of Academies of Science, Research Councils and Technology Assessment institutes in several European countries. Recently, a public panel debate in Berlin, hosted by the German Ethics Council, attracted several hundreds of people. The most extensive public involvement activity to date, is the British Synthetic Biology Dialogue, which engaged both stakeholders and citizens all over the country in a debate on synthetic biology. It resulted in a broad spectrum of conclusions. Strikingly, apart from the issues of newness and risks, most conclusions are related to the governance of science and technology in a more general sense.

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IV. Radical biology

Several bio-engineers are working on very radical concepts of biological systems; concepts that involve the fundamental principles of genetics and cellular mechanisms.

One example is the effort to add two new base-pairs or "letters" to the natural four-letter genetic alphabet by Floyd Romesberg, a chemical biologist at the Scrips Research Institute. Romesberg expects the new base pairs will be used to synthesize DNA with novel and unnatural properties.

Another method develop biological systems with unnatural properties was developed more recently by a research group from Cambridge University, in the UK. It concerns a novel system that can incorporate unnatural amino acids in biosynthesis of peptides and proteins far more efficiently than present technologies. Such entirely novel, orthogonal life-forms are also interesting because of their incompatibility with existing life-forms, which would make them relatively safe to use.

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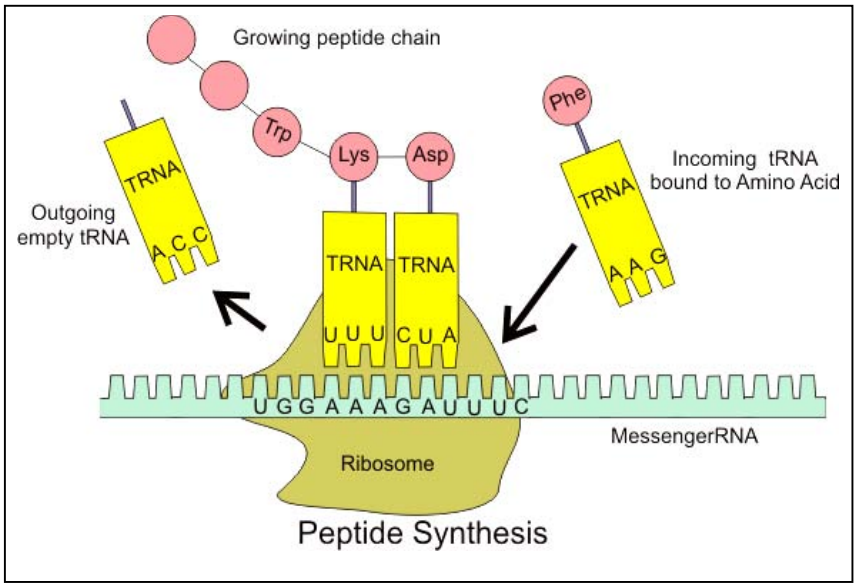
DOI: 10.1021/ja049961u

Engineered cells produce entirely new proteins

One of the ambitions of synthetic biology is the design and construction of entirely novel, orthogonal life-forms. Their incompatibility with existing life-forms would not only make such orthogonal systems relatively safe to use, they could also be designed to produce new types of proteins that can be assessed for potential medical and industrial applications.

From this perspective, the work of a research group from Cambridge University (UK), is groundbreaking. It designed a novel system that can incorporate unnatural amino acids in biosynthesis of peptides and proteins far more efficiently than present technologies.



In natural living systems, the cell's DNA is translated into proteins or peptides in three steps. First of all, the cell copies the genetic code from its DNA to messenger RNA. The

messenger RNA then takes this copy to the part of the cell that produces peptides, the ribosome.

On the ribosome so-called *triplets*, codons of three nucleotides (i.e. the building blocks of the genetic code: A, C, U or G), are linked to an amino acid (see figure).

Thus, the ribosome transcribes the genetic code step-by-step in a peptide chain or a protein. There is a total of 64 possible combinations of A, C, U and G in triplets (4^3). One of the triplets is the so-called start codon, which makes the transcription process begin. Another three triplets are stop codons that make the process end. That leaves 60 remaining triplets encoding for linkage to amino acids. Most amino acids are encoded by several different triplets. Therefore, the natural system can link only 20 different amino acids instead of 60 (see the table at the bottom of the article).

Chemical method

*Solid-phase peptide synthesis (*SPPS) was developed in the 1960's as a chemical method for creating peptides and proteins in the lab. This technology can be used to synthesize natural peptides, which are difficult to express in bacteria and to incorporate unnatural amino acids. Although SPPS is relatively simple to apply, there remain some constraints concerning the yield, length of the peptides (a maximum of 70 – 100 amino acids) and the type of peptides and proteins that can be synthesized.

Jason Chin's research group in Cambridge redesigned several pieces of the cell's protein-building machinery to construct a so-called *orthogonal ribosome*. Based on transcription of *quadruplets*, the orthogonal ribosome contains codons of four bases, and uses the cell's normal protein translation machinery. This raises the number of possible combinations of A, C, U and G to 256 (4^4) allowing the system to produce peptides and proteins with unnatural amino acids without the constraints of SPPS.

New Drugs and Polymers

Chin's team took the gene that codes for the calcium binding protein *calmodulin* and synthesized pieces of DNA designed to enhance the capability of the ribosome system, to decode quadruplets. They put this synthesized DNA in the calmodulin gene and integrated unnatural amino acids. This resulted in a protein that is more condensed and stable, allowing the protein to survive in a much wider range of environments.

Chin's research could lead to new drugs that can be swallowed without being destroyed by the acids in the digestive tract, and to polymers with entirely new characteristics for industrial uses.

Some scientists already warn that the synthesis of new proteins is not without risk. New polymers may interfere with existing cellular processes, and should therefore be carefully assessed before their use outside the lab.

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The 64 triplets (codons) and the amino acids they are encoding

Alanine	GCU, GCC, GCA, GCG	**Leucine**	UUA, UUG, CUU, CUC, CUA, CUG
Arginine	CGU, CGC, CGA, CGG, AGA, AGG	**Lysine**	AAA, AAG
Asparagine	AAU, AAC	**Methionine**	AUG
Aspartic acid	GAU, GAC	**Phenylalanine**	UUU, UUC
Cysteine	UGU, UGC	**Proline**	CCU, CCC, CCA, CCG
Glutamine	CAA, CAG	**Serine**	UCU, UCC, UCA, UCG, AGU, AGC
Glutamic acid	GAA, GAG	**Threonine**	ACU, ACC, ACA, ACG
Glycine	GGU, GGC, GGA, GGG	**Tryptophan**	UGG
Histidine	CAU, CAC	**Tyrosine**	UAU, UAC
Isoleucine	AUU, AUC, AUA	**Valine**	GUU, GUC, GUA, GUG
START	AUG	**STOP**	UAA, UGA, UAG