PRESCOUTER

SYNTHETIC BIOLOGY:

The Future of Food, Pharmaceuticals, Fuel and Chemicals

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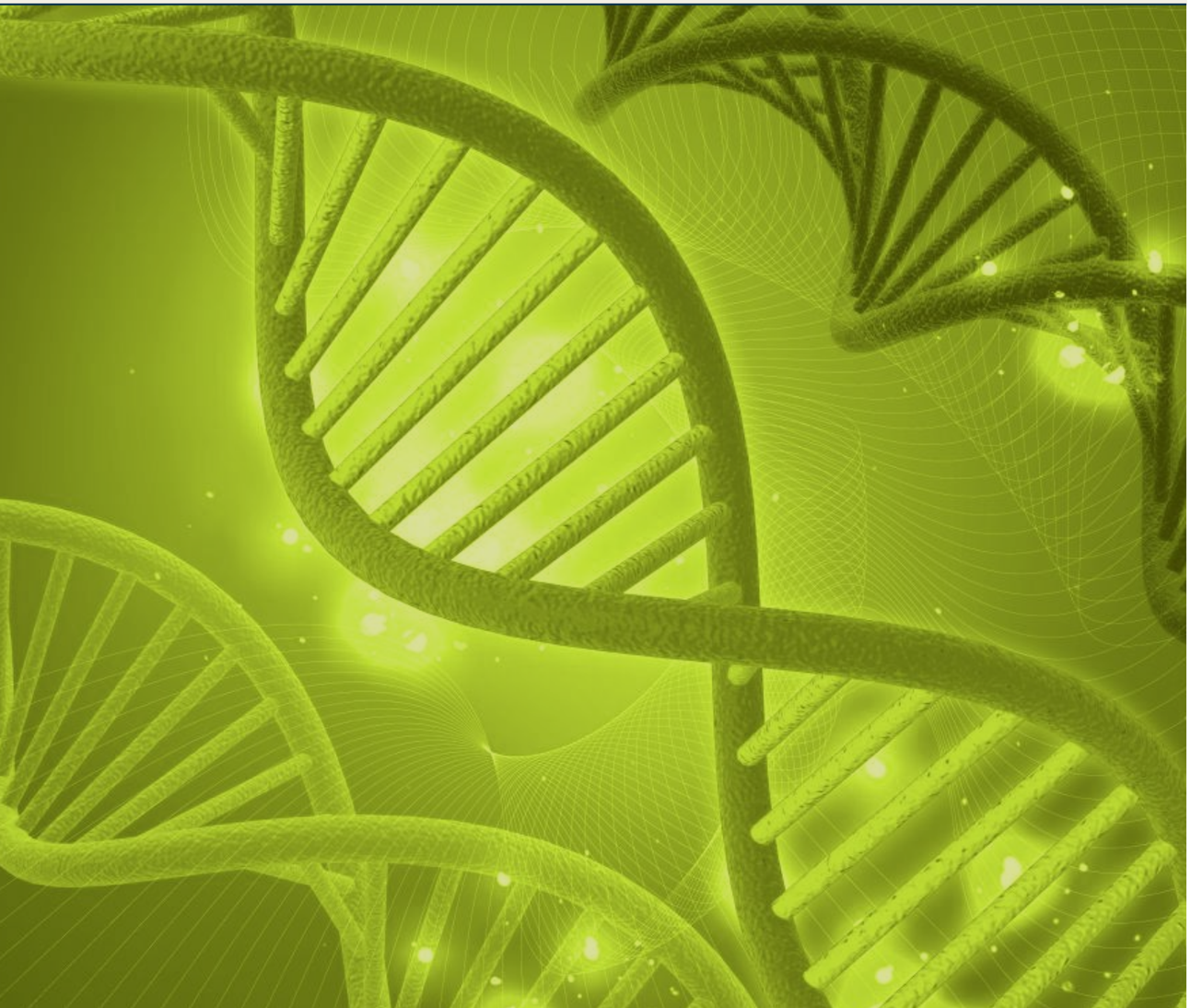
SYNTHETIC BIOLOGY:
From Then to Now



The field of synthetic biology is rapidly developing. Its aims are no less than engineering new biological systems that do not exist in nature, and redesigning existing systems from scratch. Synthetic biology lies at the intersection of engineering, biological sciences, and computational modeling, applying all these ideas and tools to designing new biological entities.

In this introductory article we present a brief chronological overview of how the field of synthetic biology has evolved, to the present day.

THE STONE AGE OF SYNTHETIC BIOLOGY: Creating and Mutating Life in a Test Tube

Using a synthetic engineering-based approach has been ubiquitous in twentieth century biology. The earliest reference to “la biologie synthétique” (or synthetic biology) is from a French professor of medicine named Stéphane Leduc (1853–1939), who coined on the term in 1912, after years of experimentation in the field. He was one of the pioneers in experimentally attempting to use synthesis as a means to understand the basic biology of organic growth and morphology. Contemporary to Leduc, John Butler Burke, a young Irish physicist working in the Cavendish laboratory in Cambridge, also tried to produce “life-like” cellular forms, mainly by plunking a bit of radium into a petri dish of bouillon. Many of the other pioneers in the field, like German-American physiologist Jacques Loeb, was interested in what Loeb called “doing something with life,” and his 1899 invention of “artificial parthenogenesis” was termed as “one of the greatest discoveries in biology”. Following the works of dutch botanist Hugo de Vries' in “The Aims of Experimental Evolution”, where he suggested that organisms might be mutated using what he called the “rays of Roentgen and Curie”, many biologists started making attempts to induce mutations in plants and later in animals. This would become known as the science of “experimental evolution.” Thomas Hunt Morgan’s studying of mutations in the Drosophilia, at Columbia in the 1910s and ‘20s, was especially instrumental. The work of Albert F. Blakeslee in the ‘20s and ‘30s established that “species could be made up to order, as it were, with a definite plan and purpose”.

THE IRON AGE OF SYNTHETIC BIOLOGY: Synthetic Biology and Genetic Engineering

Blakeslee's "genetic engineering" of the 1930's helped in the quest of creating "synthetic new species" for human purposes. In the Soviet Union, Nikolai Vavilov made efforts to improve agricultural yields, "sculpting" crops to serve humanity. In the west H. J. Muller's successes with X-ray induced mutation of the gene gained popularity, although it was not generally called "genetic engineering," then. It was also present in the thoughts of J. B. S. Haldane who claimed that "the duty of the scientist is not to explain the world but to alter the world" (Langdon-Davies 1940). And even the mid-century rise of molecular biology, historian Lily Kay has noted, had "the goal of engineering life inscribed into [its] program from its inception." She continued, noting that "this conceptualization of life as a technology was central to the empowerment of the molecular vision of life" (Kay 1993). Other notable accomplishments include Stanley Miller's famed 1953 experiment into the origin of life, and Arthur Kornberg and other's works concerning the artificial synthesis of DNA. In the 1970s, with the rise in the prominence of recombinant DNA technology, synthetic biology saw its rebirth in what was called the "new era of synthetic biology".

> **"The essence of engineering is design,"** Robert Sinsheimer wrote in 1975, **"and, thus, the essence of genetic engineering, as distinct from applied genetics, is the introduction of human design into the formulation of new genes and new genetic combinations."**
> These new methods were "supplementing" older techniques of experimental breeding.
> **"For genetic engineering one would like to be able to rejoin such fragments in arbitrary ways,"** he noted (Sinsheimer 1975)

THE NUCLEAR AGE OF SYNTHETIC BIOLOGY

The late 1990s and 2000s saw a technological boom in the field of synthetic biology. Thomas Ray had published his "An Evolutionary Approach to Synthetic Biology" in 1995, at a moment when computer coding had just begun coming into biological fields. By the late 1990s even complex biological systems were being considered for the coding of their genomes. Also by the late 1990s, Tom Knight, Gerald Sussman, Ron Weiss and other researchers published works in the field of amorphous computing, bridging the gap between earlier work in artificial life, computer science, and biocomputing. A new vision for a re-engineered biology – synthetic biology as it appears today – was emerging.

By October 2000 Carlson and Brent had drafted a letter on what they described as "open source biology" (Carlson and Brent 2000). By the following year, Carlson developed this line of thought further: "When we can successfully predict the behavior of designed biological systems, then an intentional biology will exist".

The inaugural "synthetic biology" conference, to be held in the early summer of 2004 at MIT – would later be known as "Synthetic Biology 1.0." This effort at MIT was the seed of the International Genetically Engineered Machines competition (iGEM), which allowed for a reunification of synthetic biology with genetic engineering.
Fascinating new synthetic approaches were described at the 2004 conference's successor, SB2.0, and a sense of vitality and rapid growth was prevalent. However, as various civil society groups learned about the field, they began to raise concerns about both the new bio-engineering endeavors as well as about a proposed model of "self-governance." By the arrival of the SB3.0 conference in June 2007, held in Zürich, Switzerland, the meaning of "synthetic biology" was already beginning to expand. An increasing number of researchers had learned about the field and worked to integrate their own research programs with some of its larger goals. From then until SB6.0, this time held at Imperial College in London, the conferences have seen exponential growth in both the number of participants and the research being conducted.

As synthetic biology has developed it has moved from pure trial and error to ever more systematic and controlled ways of manipulating biological organisms. Today we have the capacity to build novel organisms, with specific functionality. The subsequent articles will describe the tools used today, some of the more recent developments in the field of Synthetic Biology, and how its disruptive nature is revolutionizing the pharmaceutical, food and fossil fuel industries.

STONE AGE

1899
invention of “artificial parthenogenesis” by Jacques Loeb

1912
first recorded use of the term “Synthetic Biology” by French professor of medicine Stéphane Leduc

1920s
Albert F. Blakeslee established that “species could be made up to order, as it were, with a definite plan and purpose”

IRON AGE

1926
HJ Muller discovers X-ray induced mutation of the gene

1930s
Nikolai Vavilov made efforts to improve agricultural yields

1940
“The duty of the scientist is not to explain the world but to alter the world” J. B. S. Haldanev

1953
Stanley Miller's famed experiment into the origin of life

1970s
recombinant DNA technology, “New Era of Synthetic Biology”

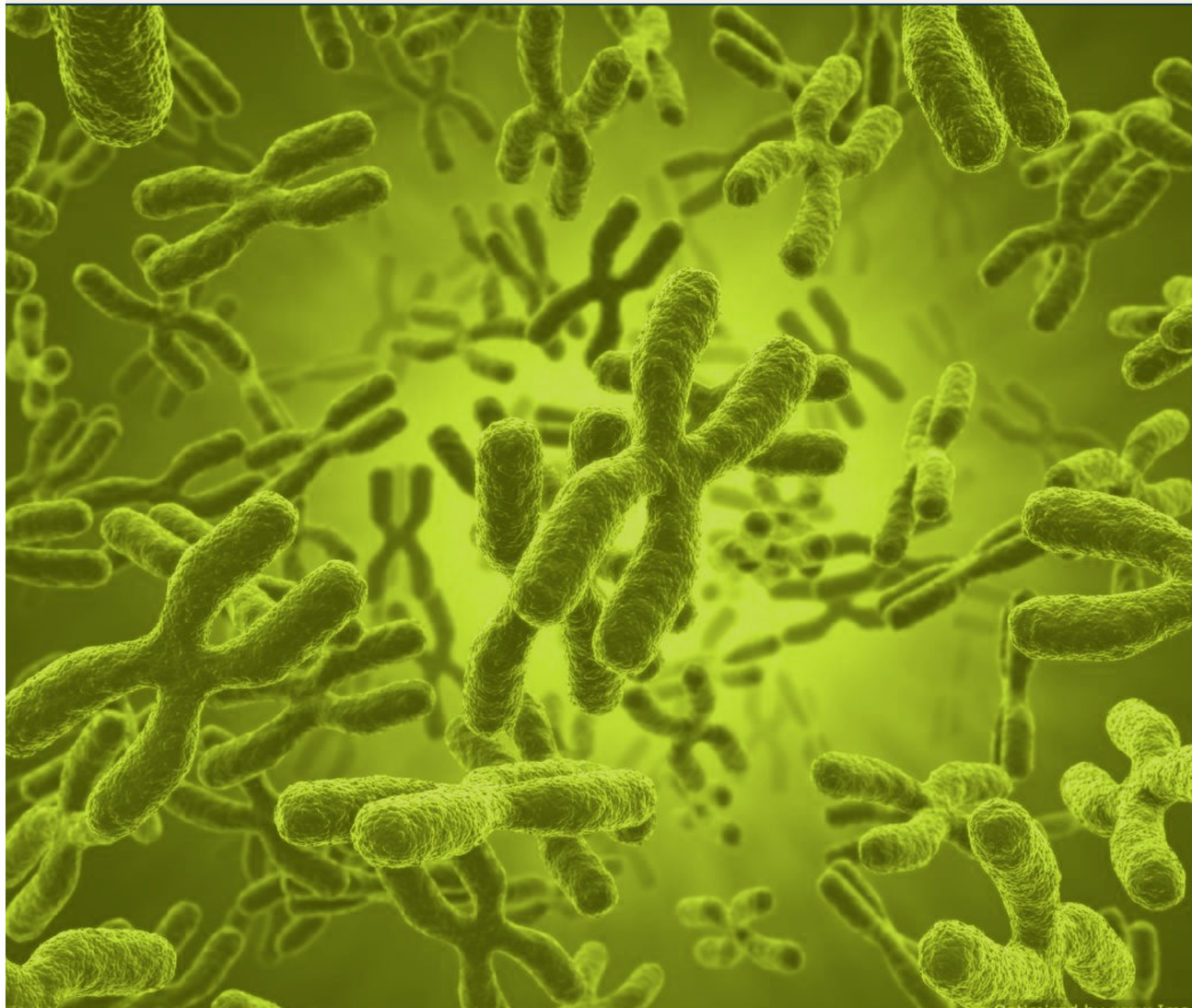
NUCLEAR AGE

1995
Thomas Ray published his “An Evolutionary Approach to Synthetic Biology”

2000
Carlson and Brent described “open source biology”

2004
“Synthetic Biology 1.0” at MIT

SYNTHETIC BIOLOGY - A Primer



SYNTHETIC BIOLOGY

Synthetic is like a toolbox, divided into two compartments; genetic engineering and re-engineering. Over the recent decades we have gained a good understanding of the genetic code and, today, that knowledge is being used by engineers to design complex living systems with significant improvements over what exists in nature!

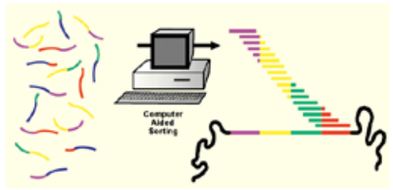
Genetic engineering

Genetic Engineering allows us to both read and modify the genetic code of organisms. However, traditionally, the methods used have been limited to trial and error, making the process time consuming and limiting the results to minor modifications of existing organisms.

Re- engineering

The next stage is to add engineering concepts to genetic technology and engineers from all fields (mechanical, computer science, chemical, biosystems, electrical etc) are working together to build efficient building blocks! We can think of this as playing and building things with LEGOs!

Sequencing



Gene sequencing allows scientist and engineers to read the genome of a target organism. The genome is cut up (using enzymes) into many small pieces and powerful computers are used to identify how those pieces fit together to make the whole genome.

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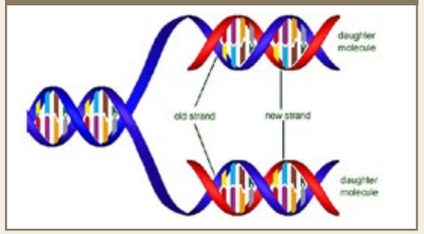


DNA is replicated by separating the two strands in the double helix. Duplicate strands are created using each individual strand as a template. This can be done as many times as needed.

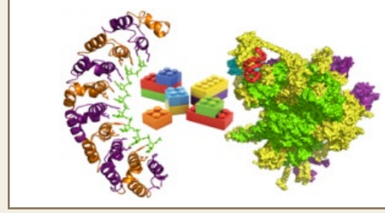
Cut and Paste

Special enzymes can cut the DNA at specific locations, leaving sticky ends. If two different DNA helices are cut with the same enzyme a section of one helix can be attached to the other. This allows the introduction of genes from one organism into other, unrelated organisms.

Computer code

Engineers treat genetic code like computer code. ATCGGACTG is equivalent to 0110011. This viewpoint, along with the ability to synthesize DNA from scratch at a low cost, allow the engineering of novel genes like programmer would write computer code.

Building blocks



Build the DNA software like Lego blocks. Can align and manipulate it online to see what the function will be, and can build it using machines much like ordering something online... Once produced, pick it up and insert it into system of choice to see if pieces of puzzle fit together.

SYNTHETIC BIOLOGY AND FOOD

As per a World Health Organization report on building a common vision for sustainable food and agriculture, the predictions for the next 35 years are frightening. "Agriculture will face an unprecedented confluence of pressures, including a 30 percent increase in the global population, intensifying competition for increasingly scarce land, water and energy resources, and the existential threat of climate change." The projected population in 2050 is approximately 9.3 billion. In order to feed the world population in 2050, we would need to increase our food production from the current 8.4 billion tons to around 13 billion tons. This increase will have to come while working with depleted natural resources such as water, due to imminent climate change, as well as land space scarcity. The dangerous trends outlined above bring about the need for alternative forms of food production.

1. IMPORTANCE OF SYNTHETIC BIOLOGY

Synthetic biology can be described as the design and development of new systems or the re-development and tweaking of current systems to produce more sustainable and efficient systems. One can think of it as breaking apart cellular components to the most basic form, selecting what we need for the problem at hand, and then putting it all back together. Or one could also think of it as choosing possible solutions for a problem, composing individual building blocks out of the solutions, and finally compiling them all together. In theory this is a powerful tool, and current research shows that it can be done to solve some of the world's most troubling issues. By 2030 we expect the population of the world to increase from 6.9 to 8.3 billion. In order to keep up with the requirements of future population needs, we need to think beyond tapping the earth's natural resources. Be it in fuel production, food processing or pharmaceuticals, advances in technology are need to ensure that we have sufficient resources for everyone.

1.1 INTRODUCTION: Food Production Environment

Originally, cheese was made using rennet extracted from an unweaned cow's stomach. In simple terms, an unweaned cow produces the enzyme rennet, which can break down milk to produce cheese. Slicing the cow's stomach, which kills the cow, extracts rennet. Starting in the 1970s, the US demand for cheese increased, from about 14.7 lb in 1970 to 25.0 lb in the 1990s (per person). People especially wanted more Parmesan and Cheddar. Rennet was originally a by-product of slaughtering young cattle for the veal industry. However, as cheese consumption increased, demand for rennet outstripped the demand for veal. The cheese industry was no longer able to sustain itself using rennet obtained from young stomachs, and needed to devise new methods of cheese production. Researchers were able to devise methodology to artificially produce rennet with the same, and perhaps even improved, qualities over natural cow rennet. They did this by genetically modifying microorganisms, which revolutionized the cheese industry. Cheese was readily available to the public at large, the costs were maintained and even vegetarians were able to consume cheese, as cattle no longer had to die in the cheese production process. This is proof of concept of a sustainable method, and one of the most important examples of synthetic biology in action.

Fast forwarding to recent years, there has been a renewed interest in sustainable food production. One of the most disruptive ideas is the production of animal and dairy products, without the use of the animals themselves. Startups and companies around the world are working with researchers to produce the perfect hamburger, or a glass of cow milk, without the cow. This is important, as growing population combined with a demand for increased standards of living and increased consumption of meat and dairy products in the developing world, fuels concerns of being able to sustain production. For example, per capita meat consumption for beef, veal and poultry has increased by 3 percent since the mid-1990s for developing countries, while the same increase has been by 0.4 percent for the developed world. When correlated to numbers, in the developing and emerging world, we get an

increase to 85 kg and for the developed world, an increase to 92 kg, per capita. When current population levels as well as growth rates are taken into account, it is the developing world that consumes more meat, in comparison to its developed counterparts. The amount of meat and dairy we produce will not be enough to sustain the growing need. There are added concerns around the impact that traditional animal production brings to the environment.

Researchers and entrepreneurs are working together to produce meat and milk that is free of these effects, aimed not towards vegetarians but towards those of us who eat meat and enjoy a good steak or hamburger. Taking this one step further, could similar alternatives be applicable to other forms of food production, and if so what are the challenges one might face? How are researchers these anticipating future challenges? Also, what kind of an economic impact will this technology have on the industry? What are the social ramifications of this technology? The following examples, and an interview with an innovator in the field, hope to answer some of these questions.

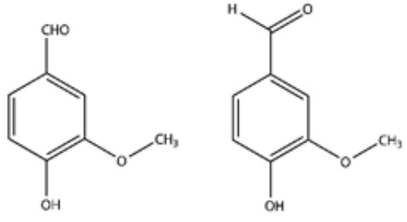
1.2 FLAVOR PRODUCTION - Vanillin, Evolva

One of the world's most common and sought after flavors is Vanillin (commonly called Vanilla), which is widely used in the food, beverage, perfume and pharmaceutical industry. Natural vanilla is a complex mixture of over 200 compounds obtained from 2 species of vanilla orchids; *Vanilla planifolia* and *Vanilla tahitensis* (Rao and Ravishankar 2000). Only about 1% of the world's annual sales of vanillin is obtained from the cured pods, and majority of it is chemically synthesized by other means. In 2010, the volume of vanillin sold annually reached more than 15,000,000 kg, 99 percent of which was obtained from chemical synthesis. The process of obtaining pure vanillin is costly, laborious, and insufficient to meet the demands of the world. Noticing the gap in supply and demand, many companies have long invested in vanillin's chemical synthesis. In recent years consumer awareness and education has led to the exploration of environmentally friendly biosynthetic applications, or the *de novo* synthesis of vanillin. Some of the examples of vanillin production can be seen in the figure below, and they consist of the bioconversion of a substrate (lignin, eugenol, ferulic acid) using a microbial organisms such as yeast, fungi or bacteria. While these processes have been largely successful, there are some drawbacks associated with using microbial hosts to carry out the bioconversion process. Some of the disadvantages are cytotoxicity of the flavors, production of undesired byproducts, expensive downstream processing based on selected substrates and products, and degradation of the desired compounds by the microorganisms.

In a nutshell, the microorganisms can be useful in the bioconversion process, provided it is a controlled reaction. One of the ways to make sure that the reaction is controlled is by using bioengineering based tools such as mutagenesis-based selection and genetic engineering of the microorganisms, for enzyme/strain optimization. Researchers at International Flavors and Fragrances, a leading flavor company, filed a patent under the topic and have aided in the bioengineering of yeast strains to produce vanillin. The core of their invention is to control the level of the byproduct by knocking out certain enzymes that lower the amount of the vanillic alcohol that forms. This increases the purity of the vanillin produced, and also decreases the associated processing costs. There are many ways to knock out the alcohol dehydrogenase enzyme and create the recombinant host, which results in the formation of vanillic alcohol as a byproduct. Methods to create the recombinant host include deletion of the entire gene, or a portion of the gene, so that it does not produce the enzyme, inserting a DNA fragment into the gene that produces the enzyme so that the enzyme is not produced (or expressed) at lower levels, or introducing one or more mutations, so as to cause a default circuit within the cells and result in no 'enzyme linked' gene expression. The DNA sequences of the associated microbe, in this case yeast *Saccheromyces cereviseae*, are available in the NCBI database for reference. *S. cereviseae* is commonly used in synthetic biology techniques, as the recombinant host cell for the production of vanillin. Since this is a commonly used microbial platform, libraries of mutants, plasmids, and detailed computer models of the cellular metabolism have been researched and are available. Given this information, production can be designed to produce an efficient process and increase yield. In this manner, a complex process is simplified, and more importantly controlled, using synthetic biology techniques.

A key aspect of using yeast in vanillin production is that yeast is completely removed from the final product. It is merely a processing aid, which results in it being excluded from GMO labeling.

Vanillin



1.3 IN VITRO MEAT

According to a 2006 report by the United Nations Food and Agriculture Organization (FAO), the meat in our diet accounts for more greenhouse gases than either transportation or industry. A 2011 study by Oxford University and the University of Amsterdam found that cultured meat would produce 96 percent less greenhouse gases and consume 82 to 96 percent less water as compared to current commercial livestock production. Cultured meat could be the perfect food of the future. In an interview for FutureFood 2050, Israeli biomedical engineer Amit Gefen says, "you can control the nutritional value and the amount of chemicals and antibiotics so you can minimize their effect on the human body". The factor of taste can also be controlled, by co-culturing and combining chicken cells with fat cells to produce the perfect level of juiciness.

Thus we could imagine that a modern bioreactor could soon replace the slaughterhouse. How would a bioreactor function to produce meat? The general idea is to select stem cells and allow them to proliferate in the bio-reactor.

> Israeli biomedical engineer Amit Gefen says, **"you can control the nutritional value and the amount of chemicals and antibiotics so you can minimize their effect on the human body".**

Using a bio reactor would ensure a controlled process in both bio-conversion and amplification. The type of stem cells most commonly used are skeletal muscle progenitor cells and mesenchymal stem cells, both of which are easier to isolate from animals and more importantly have high proliferation rates. Once the cells are in the bioreactor and ready to grow, they would need the right environment, which can be controlled by gas levels, temperature, humidity, sterility and the right substrate. Electrical, mechanical, physical and biochemical stimulation would result in the proliferated cells resembling a muscle tissue. While research is progressing at a rapid pace, it will still be a few years before commercial production of in vitro meat begins. Researchers in Europe and Iran are finding ways to produce lab grown hamburger and chicken meat, to help the world produce meat in a sustainable way. Professor Amit Gefen, from Tel Aviv University and quoted above, has begun a $25,000 feasibility study on developing chicken meat in a lab, funded by the Modern Agriculture Foundation. The difference between his research and that done by Maastricht University in the Netherlands (2013) around producing a $300,000 lab grown beef patty, is the method of production. The hamburger patty has cow fibers all aligned together to produce a beef patty, while Israeli researchers are working to produce chicken meat from a single cell. The cultured chicken cells will then divide and multiply. They hope to have the methodology figured out by the end of the year.

The beef patty was originally valued at $300,000 but the current cost is $11.36. So advances in research lead to more economically viable in-vitro meat production and a niche market waiting to be captured. Currently they predict that mass commercialization of cultured meat could take anywhere between 10 to 30 years, depending on how well initial experiments work.

1.4 RICE PADDIES

Atmospheric methane is the second most important greenhouse gas after carbon dioxide, and is responsible for 20 percent of global warming. One of the main contributing factors to methane production is rice paddies, which produce up to 17 percent of global methane. This, coupled with the sustained increases in rice production (as rice is a staple carbohydrate in the vast majority of the world) results in 25 to 100 million tons of methane derived annually from rice cultivation. Researchers at the Swedish University of Agricultural Science, Uppsala, have produced a new type of rice that is higher in starch and has significantly lower methane production. SUSIBA2 rice is the first rice to be high yield and low methane producing, and could offer a sustainable solution to the problem. They achieved the new type of rice by the addition of a single transcription factor gene derived from barley, which conferred a shift of carbon flux. This single addition creates a change in allocation of the photosynthates (photosynthetically derived sugars) which results in a higher biomass presence above the ground. SUSIBA2 cut methane emissions to around 10 percent of control levels before flowering, and almost to zero at 28 days after flowering. In addition SUSIBA2 has fewer methane producing areas, methanogens, around the roots. As the researchers point out, this new innovative approach will be beneficial in combatting climate change and increasing world temperatures.

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2. MUUFRI - Interview with Perumal Gandhi

Perumal and Ryan co-founded Muufri (Moo-free) because they wanted to make the world's food system a better place. It is their belief that the world we live in today values quantity over quality. As a part of their foundation, they are trying to produce milk from yeast cells by a simple fermentation process. This can be thought of as craft milk production, similar to craft breweries. In essence the fermentation based process uses yeast to convert a carbon source to milk proteins. Yeast is trained to think like cow cells and produce milk. To the resulting milk protein, other milk components such as fat, water and added nutrients are added after fermentation, thus creating milk as we know it.

What are differences between milk and muufri milk, functionality and taste wise?

> "Cow milk protein and protein from Muufri are functionally nearly the same. There is no lactose in Muufri milk. The taste will be different based on the raw material. We hope that people will be able to brew their own milk in a similar manner to craft brewing."

Would a consumer have options of low fat, skim, chocolate milk, butter or cheese?

> "Yes! The Muufri milk will be not different from regular milk in functionality."

What is the shelf stability of the milk, given that you are using yeast cultures?

> "Expect the milk to be shelf stable, and a sterile product. Since the research is at a nascent stage, and they have extracted some muufri based milk proteins it will still take time to scale up the process and do physical, microbiological and shelf stability tests on the milk."

Overall, what do you think is the future of synthetic biology? What do you think are some of the challenges you might face?

> "Synthetic Biology is a quantum leap in the food industry! The main caveats are consumer perception and government and regulatory standing on the foods. In the food industry (unlike pharmaceutical and fuel industries) the main market driver is consumer perception. A great idea can go bust if a consumer does not support it."

Perumal also pointed out that he would like for it to be called Applied Biology, and not Synthetic Biology, as the term Synthetic connotates something fake, which it is not. And it clearly does not help consumer perception.

They are working to produce a great product, and we look forward to tasting Muufri and buying it off the grocery shelves!

SYNTHETIC BIOLOGY:

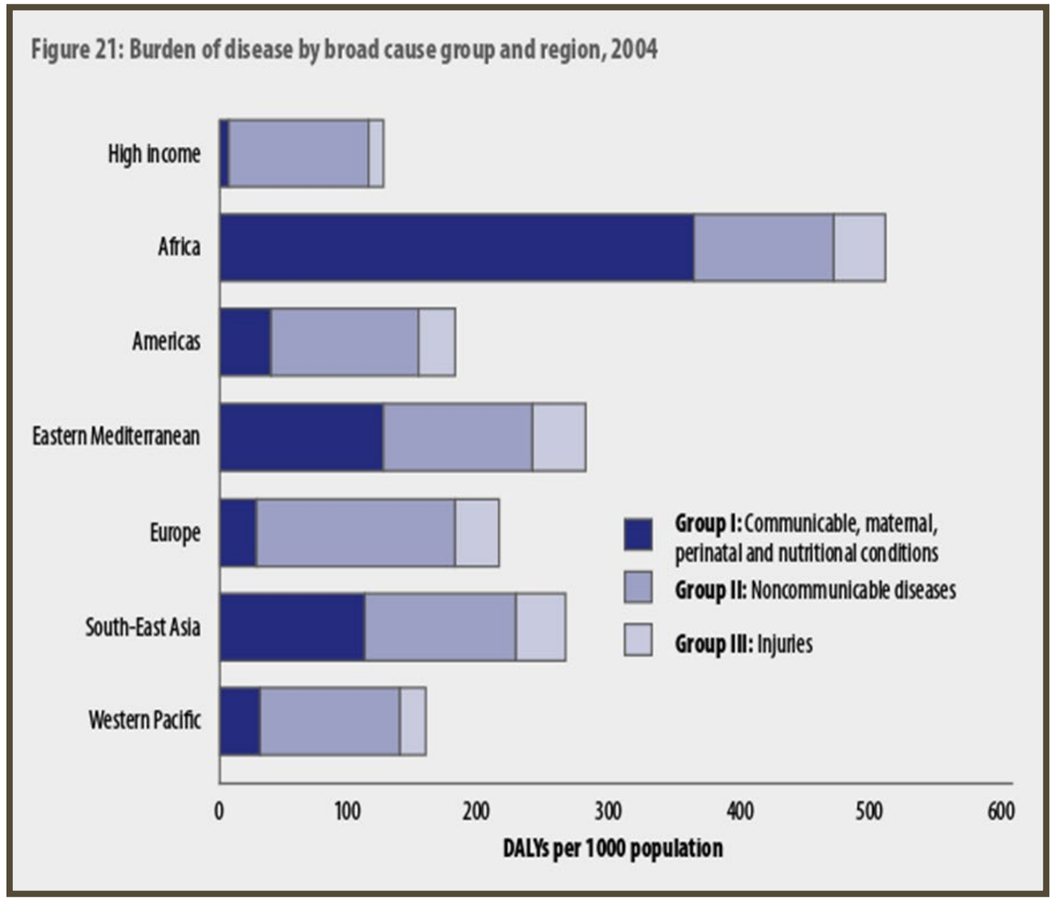
A Breakthrough in Pharmaceuticals

1.1 INTRODUCTION

The World Health Organization (WHO) defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO 1946)). Though medical progress has led to considerable improvements in human well-being, a huge potential for further improvements still remains. Disability-adjusted-life-years (DALY) measure the years of life lost due to premature mortality, plus the weighted number of years lived with disability or reduced well-being (the weights depend on the severity of the condition). The worldwide DALY for the year 2004 was calculated as 1.52 billion (WHO 2008), amounting (with a global population of 6.44 billion) to an average of 0.24 years per person.

Figure 27: Ten leading causes of burden of disease, world, 2004 and 2030

2004 Disease or injury	As % of total DALYs	Rank	Rank	As % of total DALYs	2030 Disease or injury
Lower respiratory infections	6.2	1	1	6.2	Unipolar depressive disorders
Diarrhoeal diseases	4.8	2	2	5.5	Ischaemic heart disease
Unipolar depressive disorders	4.3	3	3	4.9	Road traffic accidents
Ischaemic heart disease	4.1	4	4	4.3	Cerebrovascular disease
HIV/AIDS	3.8	5	5	3.8	COPD
Cerebrovascular disease	3.1	6	6	3.2	Lower respiratory infections
Prematurity and low birth weight	2.9	7	7	2.9	Hearing loss, adult onset
Birth asphyxia and birth trauma	2.7	8	8	2.7	Refractive errors
Road traffic accidents	2.7	9	9	2.5	HIV/AIDS
Neonatal infections and other[a]	2.7	10	10	2.3	Diabetes mellitus
COPD	2.0	13	11	1.9	Neonatal infections and other[a]
Refractive errors	1.8	14	12	1.9	Prematurity and low birth weight
Hearing loss, adult onset	1.8	15	15	1.9	Birth asphyxia and birth trauma
Diabetes mellitus	1.3	19	18	1.6	Diarrhoeal diseases



With simple assumptions this results to an average loss of 16 healthy years during a lifetime due to disabling diseases or premature death. Also, considering the costs associated with such diseases, data shows that the most costly ones in the U.S. (2009) in terms of total cost are heart and cardiovascular diseases (USD 475 billion), alcohol abuse and dependence (USD 301 billion), digestive diseases (USD 260 billion), cancer (USD 240 billion), and mental diseases (USD 217 billion) (Kockaya 2010). The top four categories of disease thus account for more than USD 1.275 trillion per year.

Table 3. The list of top 5 most direct costly diseases.

Diseases	Direct Costs (in billion US dollars)
Heart & CVD	313.8
Digestive Diseases	220.8
Mental Diseases	175.7
Diseases of the Nervous System	153.3
Diabetes	128.3

Table 4. The list of top 5 most indirect costly diseases.

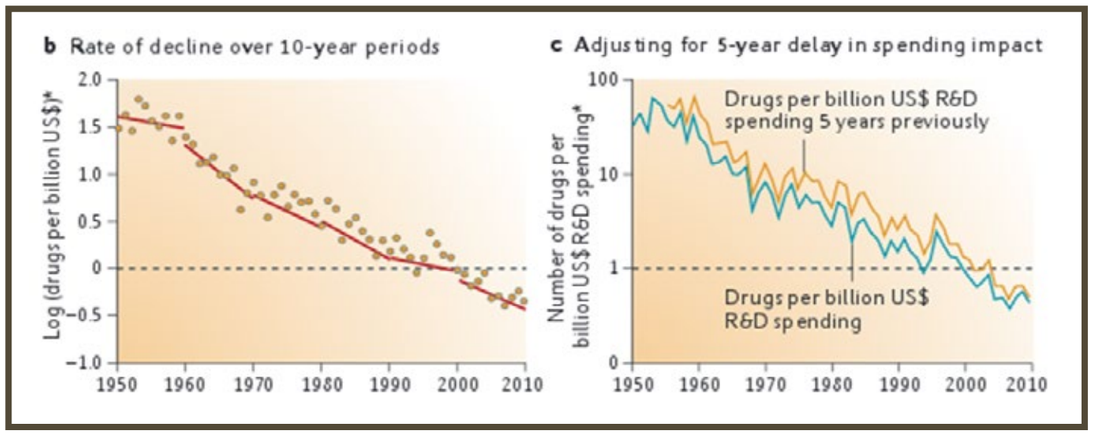
Diseases	Direct Costs (in billion US dollars)
Alcohol Abuse and Dependence	218.5
Heart & CVD	161.4
Cancer	141.5
Tobacco(Smoking)-Related Death and Disease	101.85
Alzheimer	94

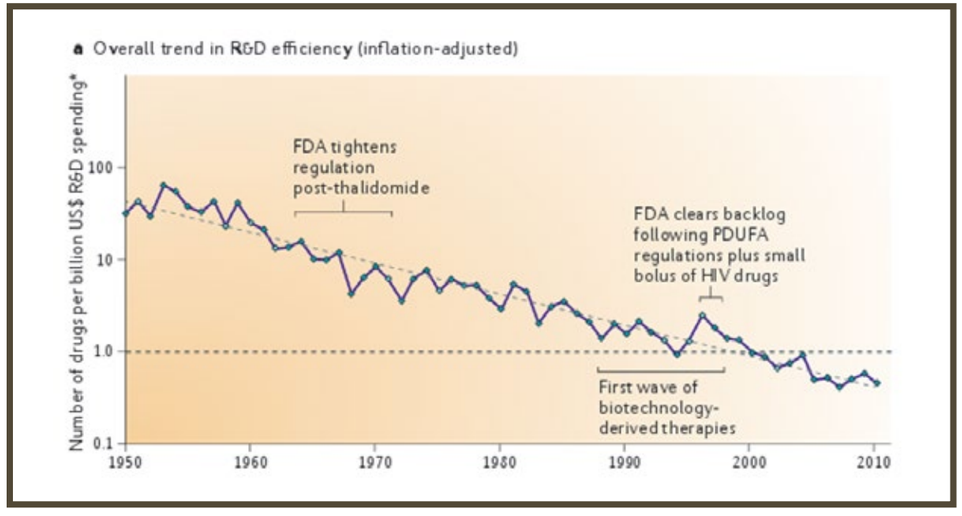
Table 5. The list of top 5 most total cost diseases.

Diseases	Direct Costs (in billion US dollars)
Heart & CVD	475.3
Alcohol Abuse and Dependence	300.6
Digestive Diseases	259.6
Cancer	239.5
Mental Diseases	216.6

1.2 CURRENT HURDLES IN THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry's potential for improving human health is affected by a twofold challenge with respect to innovation, which increases cost and reduces returns. In the past 60 years the pharmaceutical industry has seen major scientific and technological advances. But this industry is faced with "Eroom's law," which states that the number of new drugs approved per billion US dollars has halved every 9 years since 1950 (Scannell et al. 2012). Eroom's law corresponds to an average annual cost increase of 8 percent. (DiMasi et al. 2003) reports similar results, concluding that "total capitalized costs were shown to have increased at an annual rate of 7.4 percent above general price inflation." Other estimates even yield compound annual growth rates of such costs to more than 13 percent (Munos 2009). As Dickson and Gagnon (2004) state: "Since the mid-1960s, the process of drug approval has been modified to significantly improve the safety and efficacy of drugs for use by the general public. A consequence of these scientific and regulatory changes has been an increase in the time and cost of bringing a new drug to market." Furthermore, in order to avoid intense product-market competition firms tend to direct their R&D [research and development] investments toward new therapeutic targets characterized by high uncertainty (Pammolli et al. 2011). Pammolli and coauthors conclude that "this reorienting of investments accounts for most of the recent decline in productivity in pharmaceutical R&D." The increase in the time to market mentioned above directly affects the second challenge, which are reduced returns for innovation. Patent protection for pharmaceuticals lasts a maximum of 25 years. On average, about half of this time will be over when the new drug finally hits the market (e.g., DiMasi et al. 2003).





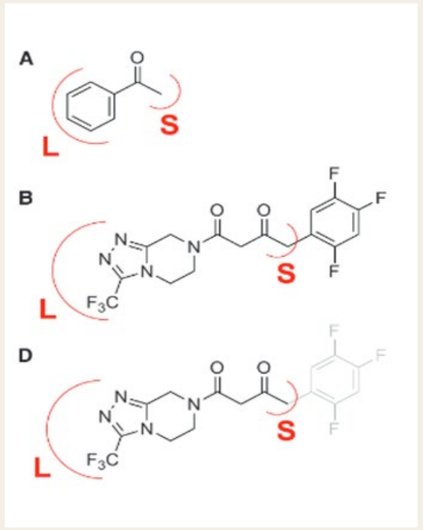
On Jan. 7, 2015 when researchers announced the discovery of teixobactin, it was the first new antibiotic in 25 years! Though it was tested only in animals, it could be the solution against antibiotic-resistant bacteria. A report from the Pharmaceutical Research and Manufacturers of America (PhRMA) says that between 1998 and 2014, just 7 therapeutics won the FDA approval for treatment of melanoma, while 96 of them were either "discontinued," "suspended" or had "no development recorded". Considering the low approval rate, it is no surprise that the price for successful therapies today is $1.2 billion or more, as compared to $800 million in 1990's. With the price of failure higher than ever, the drug developers want to make the drug development process as efficient as possible. This has resulted in a fundamental change the way pharmaceutical R&D has been done.

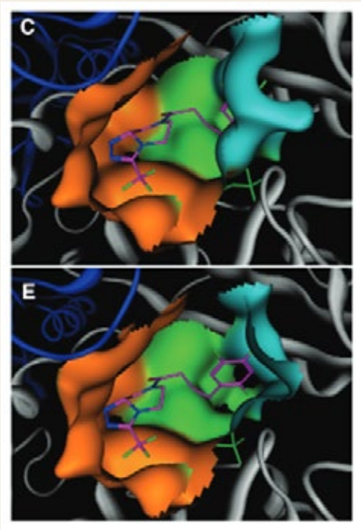
1.3 SYNTHETIC BIOLOGY IN HEALTHCARE INDUSTRY

To assess if and how synthetic biology might help to address this innovation challenge going forward we consider three already existing applications in the field of pharmaceuticals: Sitagliptin, Cephalexin, and Artemisinin.

CASE 1: Sitagliptin

The synthesis of drugs can benefit greatly from the selectivity associated with enzymatic catalysis. The company Codexis has designed efficient biocatalytic processes, to replace the rhodium-catalyzed asymmetric enamine hydrogenation for large-scale manufacture of the anti-diabetic compound sitagliptin. The starting enzyme had the catalytic machinery to perform the desired chemistry but lacked any activity toward the prositagliptin ketone. The authors from Codexis applied a substrate walking, modeling, and mutation approach to create a transaminase with marginal activity for the synthesis of the chiral amine. This variant was then engineered for large scale manufacture using directed evolution. The resultant biocatalysts showed broad applicability toward the synthesis of chiral-amines, previously accessible only via resolution. This work underscores the maturation of biocatalysis to enable efficient, economical, and environmentally benign processes for the manufacture of pharmaceuticals. In a paper in *Science* on the project, Merck and Codexis reported a 10-13% increase in overall yield, a 53% increase in productivity and a 19% reduction in total waste.





"Active site of transaminase consists of large (L) and small (S, typically limited to substituents about the size of a methyl group) binding pockets as mapped on the structure of acetophenone (A). Accordingly, the structure of prositagliptin ketone (B) can be mapped on these binding pockets and docked into the active site of the homology model (C). A prositagliptin ketone analog (D) was designed to fit the large pocket for initial optimization of this part of the active site. After initial engineering of the large pocket, an enzyme variant was generated with activity on the desired substrate (E) by excavating the small pocket (gray/blue, transaminase homology model; orange, large binding pocket; turquoise, small binding pocket; green, PLP and catalytic residues)."

"Although naturally occurring enzymes rarely offer ideal manufacturing catalysts, directed evolution provides an effective means to overcome this limitation. We have demonstrated that combining modeling with directed evolution offers a rapid means of creating an active enzyme that can operate under the demanding conditions required for the manufacture of pharmaceuticals. This development will serve as a model for the implementation of other biocatalytic manufacturing processes in which enzymes can be evolved to meet desired chiral process targets."

This achievement earned the innovators the 2010 Presidential Green Chemistry Challenge Award: “This collaboration has led to an enzymatic process that reduces waste, improves yield and safety, and eliminates the need for a metal catalyst.” (U.S. Environmental Protection Agency).

"Codexis is honored to receive one of the U.S. government's highest awards for environmental protection with Merck," said Alan Shaw, Ph.D., Codexis President and CEO. "Our proven technology platform is in use around the world, enabling creation of cleaner, more efficient pharmaceutical manufacturing processes. We are committed, with our colleagues at Merck, to leveraging the power of green chemistry for a sustainable environment."

CODEXIS®

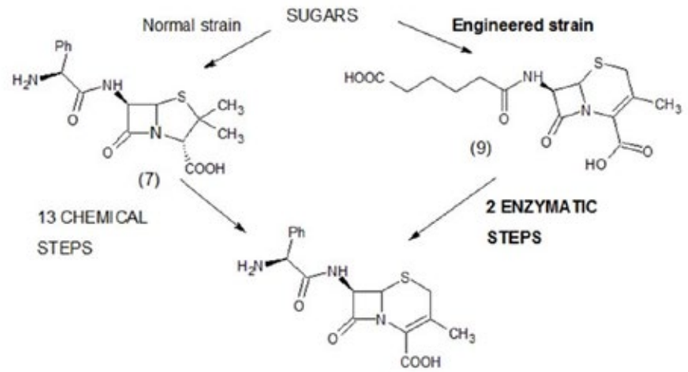
MERCK

CASE 2: Cephalexin

The company DSM’s application of synthetic biology methods to the production of Cephalexin is quite similar to the first example.

From 1975 to 1985, cephalexin was produced by a 10-step process, using conventional methods of chemistry and generating waste of around 30-40 kg per 1 kg of product. In 1985 the waste to product ratio was reduced to 15 after a lengthy process of optimization, and the introduction of recycling. In 1995, Chemferm introduced a 6-step process to produce cephalexin, that applied biocatalysis in a three step reaction and reduced the waste ratio to 10.

But later, starting with a penicillin-producing microbial strain, DSM introduced and optimized two heterologous genes encoding acyl transferase and expandas respectively for a one-step direct fermentation of adipoyl-7-ADCA. This product was then converted into Cephalexin via two enzymatic steps, replacing a process requiring 13 chemical steps. The improved process is reported to save 65 percent



of energy and materials and to cut costs by 50 percent. Besides reducing the quantity of waste, toxicity was also significantly decreased. The original processes needed methylene chloride, silylating agents, Dane-salt protected side chains and acylating promoters. But the new process mainly released aqueous waste streams, containing harmless inorganic salts.

Both DSM and Gist-Brocades had expertise in complementary fields. GB had great depth of knowledge in microbiology and genetics (strain selection and improvement, over-expression of enzymes, introduction of new enzyme activity to enhance or introduce metabolite production), biochemistry (identification of bottlenecks in metabolism and characterization of enzymes) and fermentation. DSM could contribute its experience in bio-catalysis and organic chemistry in intermediates. There was considerable pressure from various Asian and Indian antibiotic companies on the market share, which led to the two companies creating a joint venture called Chemferm.

Despite the promising market prospects of this new technology, which allowed reactions to generate less waste, it was difficult to raise funds for R&D. The company managed to reduce operating costs by using more efficient bio-catalytic processes. There were several steps in the process design, including; screening existing enzymes, strain selection, strain improvement, optimization of the fermentation process, choice of enzyme, bioreactor type and optimization of the downstream processing and product isolation.

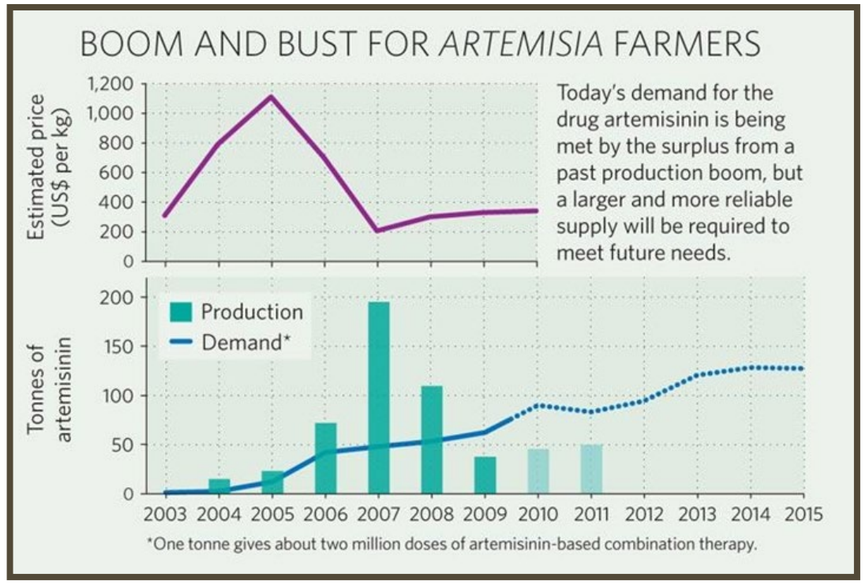
DSM

CASE 3: Artemisinin

Malaria produces 300–500 million new infections and 1–3 million deaths each year in areas of poverty. The majority of the disease burden falls on African children younger than 5 years of age.Due to widespread and unsupervised use of malaria drugs, chloroquine-resistant *P. falciparum* emerged in the early 1960s and spread rapidly around the world. Today there are reported cases of Plasmodium parasite resistance to most of the currently available antimalarial therapies, thus necessitating the development of new treatments. A new class of antimalarials were first isolated and developed in China in the 1980s using the antimalarial properties of the plant *Artemisia annua*, or sweet wormwood, called *qinghao* in Chinese. Artemisinin so obtained from the plant can be chemically converted into several active derivatives. Artemisinin derivatives such as artesunate, artemether, and dihydro-artemisinin (DHA) are extremely potent antimalarials that act rapidly against both the parasite's asexual and sexual stages, which could potentially help reduce the rate of malaria transmission. In addition, artemisinin-derived drugs have been shown to be highly effective against parasites that are resistant to other antimalarial drugs. The World Health Organization first endorsed ACTs for the treatment of malaria in 2004, and recommended a switch to the drugs as the first-line malaria treatment in 2005.

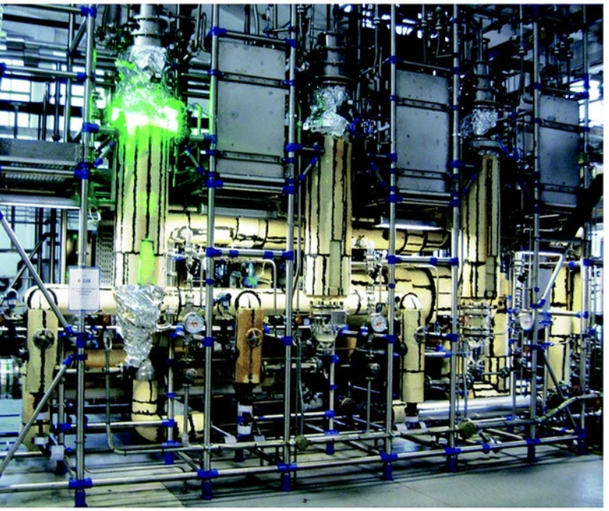
A. annua is a very labor-intensive crop with a lengthy growing cycle. The time in between the crop growth and artemisinin extraction can be between 12 and 18 months. The commonly accepted artemisinin recovery yield is approximately 5 kg per 1,000 kg of dry leaves, produced from around 1 hectare (ha) of *A. annua* plants. Based on this yield, an estimated 17,000 ha are required to produce enough artemisinin to manufacture 100 million adult treatments per year. In 2004, there was only an estimated 4,700 ha of Artemisia grown in the world, mainly located in China and Vietnam. Efforts to scale-up the cultivation of *A. annua* in Asia and East Africa are forecasted to increase the total acreage to around 11,200 ha.

However, an additional source for artemisinin production was clearly required to meet projections of a global demand of 400 million ACT treatments per year. Owing to the sensitivity of the crop to genetic backgrounds, cultivation conditions, and harvesting periods, and the scarcity of growing area, the high cost of producing artemisinin itself (reported to be a range of $900–$1,600/kg in 2006; Boston Consulting Group) was the key cost driver for ACTs.



The genetic engineering and recombinant DNA technology revolutions have profoundly changed modern medicine. Recombinant proteins are produced through genetic engineering of microorganisms, which can be industrially fermented to produce copious amounts of pure and potent biotherapeutics at a lower cost. Professor Jay Keasling's laboratory at the University of California, Berkeley, and scientists at Amyris Biotechnologies proposed the use of synthetic biology to develop strains of *Saccharomyces cerevisiae* (baker's yeast) for the high-yielding biological production of artemisinic acid, a precursor of artemisinins. Earlier attempts had been made to produce commercially relevant concentrations of artemisinic acid, but were unsuccessful, and led to production of only 1.6 grams per litre of artemisinic acid. However, by using a complete biosynthetic pathway they have produced 25 grams per litre of artemisinic acid. This pathway included the discovery of a plant dehydrogenase and a second cytochrome that provide an efficient biosynthetic route to artemisinic acid, They also reported a

well-developed, practical, efficient and scalable chemical process for the conversion of artemisinic acid to artemisinin using a chemical source of singlet oxygen. This avoids the need for specialized photochemical equipment.



To effectively steer these efforts and to maximize the project probability of success, OneWorld Health and the Bill & Melinda Gates Foundation worked with Amyris Biotechnologies and the Keasling laboratory to determine the best overall product development strategy. They determined the criteria to move the project forward and what future partnerships were needed to transition the research and laboratory-scale development work to pilot-scale and eventually manufacture at a commercial scale. In addition, One-World Health developed a commercialization strategy based on a thorough understanding of the worldwide regulatory requirements and an analysis of the current ACT manufacturing supply chain and distribution model. The outcome of this analysis allowed OneWorld Health to select scale-up and manufacturing partners that will maximize the impact of the semi-synthetic artemisinin on global ACT pricing.

In 2008, Amyris made available its Artemisinic Acid-producing yeast strains to Sanofi, via OneWorld Health, on a royalty-free basis. Sanofi now uses this technology at large-scale to produce Artemisinin for ACT treatments. More than 1.7 million treatments of Sanofi's ArteSunate AmodiaQuine Winthrop® (ASAQ Winthrop, fixed dose artemisinin-based combination therapy), manufactured with semisynthetic artesunate in Morocco, were shipped from Sanofi's distribution center to Burkina Faso, Burundi, the Democratic Republic of the Congo, Liberia, Niger, and Nigeria, starting in August 2014.

AMYRIS

SANOFI

"This shipment represents a critical step in improving access to effective treatments and combating malaria in some of the most affected countries in the world," said Dr. Robert Sebbag, vice president of Sanofi's Access to Medicines. **"Sanofi is proud that these first batches of antimalarial medicines produced with semisynthetic artemisinin derivative are on the way to reaching patients. This milestone is the result of the enduring partnership between PATH (a leader in global health innovation) and Sanofi that has translated years of effort into lifesaving change."**

Both artesunate (the active ingredient produced from semisynthetic artemisinin) and semisynthetic artemisinin itself have been proven identical to those derived from botanical sources. Consequently, there are no changes to the quality of ASAQ Winthrop®.

"Semisynthetic artemisinin demonstrates how public-private partnerships, tenacity, and an urgent and shared goal—saving children's lives—can drive promising innovations to transformative global scale," says Steve Davis, president and CEO of PATH. **"As we work together toward a world free of malaria, we are thrilled to see this cutting-edge technology reach the people whose lives it can save. We are proud to join Sanofi and our partners in celebrating this achievement."**

1.4 How Synthetic Biology can help overcome Pharmaceutical Industry's Problems

Synthetic Biology applies an understanding of disease mechanisms to drug discovery, and of screening mechanisms to therapeutic solutions. They help improve the production process of the existing drugs, which results in cost savings, and carries an added environmental advantage by reducing waste output. This alleviates the problem of exponential increases in the development costs of new drugs.

Synthetic Biology may also offer new methods of drug discovery and the potential for entirely new therapeutic approaches, solutions which differ radically from existing treatments. This would greatly help set the pricing strategies of drugs, helping pharmaceuticals overcome the double challenge described at the beginning of this article.

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Synthetic Biology Disruptive Technologies

in the Renewable Fuel and Chemical Sectors

It is widely recognized that dramatic change is needed with respect to the use of fossil fuels. Petroleum reserves are decreasing and climate change presents imminent and increasing risks to both environmental and human health. Yet, as a scientific community, we have struggled to address these problems on a global scale. Synthetic biology is a powerful tool that is currently being used to enable the transition from a fossil fuel-based economy to a biomass-based economy.

Biofuels are a high priority use for synthetic biology as there are major pollution and pricing instability concerns related to fossil fuels. The U.S. Department of Energy (DOE) has spent millions of dollars in the past few years on synthetic biology research. First generation biofuels (for example, ethanol derived from corn, wheat and sorghum starch; biodiesel derived from vegetable oils) have proved to be unsustainable due to extensive water usage and the potential stress on food commodities from land competition. In spite of these impediments, research is constantly on-going to make first generation biofuel production sustainable. One example would be that of Amyris Biotechnologies. They have set up a plant in Brazil in collaboration with BP, Shell and French oil company Total. There they are using their proprietary synthetic yeast to produce enzymes that break down sugarcane into fuel even more efficiently than the traditional processes that have been followed for the past 4 decades in the world's biggest alternative fuel economy..

1. BIOFUELS

Next generation biofuels generated from non-food sources or cellulosic biomass such as switchgrass and miscanthus, have the potential to relieve the pressure on agriculture. POET-DSM Advanced Biofuels joint venture began in 2012 and reached its first significant milestone in 2014 with the grand opening of a new production plant in Iowa. Commercialization of cellulosic ethanol has remained a major challenge, due to inefficiency in co-fermenting C6 and C5 sugars (xylose and arabinose). However the development of synthetic enzymes and robust industrial yeast strains have optimized conversion rates. This is one effort that has resulted in the production of cellulosic ethanol at an industrially relevant scale.

Scientists are now engineering algae cells to make them secrete fuel intermediates (such as lipids and fatty acids) that can then further be refined into fuels. This is an exceptionally lucrative technology due to the ability of algae cells to grow by capturing solar energy and CO2 and utilizing waste resources such as municipal water. Algae's relatively simple genetic background renders it easy to manipulate. US-DOE invested $25 million last year and $18 million this year in order to improve the economics of producing biofuel from algae. Their goal is to reduce the modeled price to less than $5 per gasoline gallon equivalent (gge) by 2019 and to less than $3 gge by 2030. ExxonMobil contributed $600 million to Venter's new startup company, Synthetic Genomics, Inc., with the aim of extracting "biocrude" from photosynthetic algae that can then be refined into gasoline, diesel, and jet fuel.

Another company to look out for in the sector of algal oils and bioproducts is Solazyme, which is transforming algae using synthetic biology tools. It has commercialized Encapso, a biodegradable encapsulated lubricant for drilling fluids, whose effectiveness has been demonstrated in 30 oil wells in basins across United States and Canada. Besides that, it has commercialized food ingredients such as high oleic fatty acids, whole algal protein, and flour after successfully having passed US FDA's GRAS specifications. Companies such as Natura and Unilever are now using microalgal oil, produced by Solazyme, in their cosmetic and personal care products. These products are just coming to market, with over 65 active applications, more than half of which were developed this year alone. And this innovation has led to impressive financial results. Solazyme earned $8.8 million in product revenue in the first quarter of 2015, up 20 percent from the same period in 2014.

2. BIOCHEMICALS

Fossil fuels are not only consumed directly for energy, but also converted to a range of chemicals and other products such as rubber, plastic, food additives, cosmetics and more. Synthetic biology has an important role to play in these uses as well.

Isoprene and Rubber

From 2000 to 2013, the total global production of synthetic rubber increased from 11 to 15.5 million metric tons, while that of natural rubber increased from 7 to 12 million metric tons. It's fairly easy to imagine the extensive exploitation of natural resources and non-renewable fossil fuels needed for the production of that quantity of rubber. The collaborative research agreement between Genencor (now DuPont) and The Goodyear Tire and Rubber Company in 2008 to develop BioIsoprene from renewable raw materials came as a major breakthrough. The goal was to make the rubber and tire industry less dependent on petroleum-derived isoprene monomer, and also to reduce the carbon footprint of the synthetic rubber production process. Isoprene can either be polymerized into rubber for making tires (consuming 70 percent of the world isoprene production in 2013) or it can be used for making adhesives (a 20 percent market share in 2013) and various other specialty chemicals. Considering that the majority isoprene is used in tire rubber production, it is not surprising that synthetic biology is now being used to make this high commodity chemical. Progress is evident from the recent partnerships between major downstream rubber players and biochemical companies (ex. Ajinomoto-Bridgestone and Amyris-Michelin). Other companies developing fermentative isoprene production are GlycosBios, Aemetis and LanzaTech.

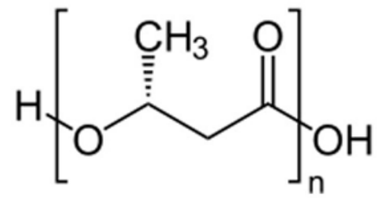
Referring specifically to the DuPont-Goodyear merger, a high efficiency fermentation process has been developed and genetically engineered microbial strains have been optimized to contain and express plant genes that encode the enzyme (Isoprene Synthase) and thereby convert glucose into isoprene. The first demonstration tires made with BioIsoprene technology were showcased at the 2009 United Nations Climate Change Conference, in Copenhagen. This technology is continuously being refined to improve production efficiency through developments in synthetic biology. Commercial production of BioIsoprene monomer was listed as one of DuPont Industrial BioSciences' milestones for 2014-2016 in Biofuels Digest, 2014 edition.

Acrylic

Acrylic is another important industrial chemical, used in a wide range of industrial and consumer products such as paints, adhesives, diapers and detergents. Petroleum based acrylic is currently a $10 billion industry. OPX Biotechnologies has successfully produced BioAcrylic using a proprietary technology called EDGE (Efficiency Directed Genome Engineering) that enables the complete genetic redesigning of a natural strain for the economic production of BioAcrylic from sugar. The sugar is derived from renewable sources such as corn, sugarcane and non-food cellulosic biomass. OPXBIO, along with The Dow Chemical Company – the largest U.S. producer of petro-acrylic – has scaled up the bioprocess to pre-commercial demonstration scale. They are set to start commercial scale production by 2018. Besides that, OPXBIO anticipates that commercial quantities of specific fatty acids with applications in personal care products, flavors and fragrances, as well as cleaning products and lubricants, will be available in 2016. It has also partnered with Evonik Industries AG to develop the process of making bio-based specialty chemicals using the EDGE platform. As a result of these promising results, OPXBIO was acquired by Cargill in April of 2015.

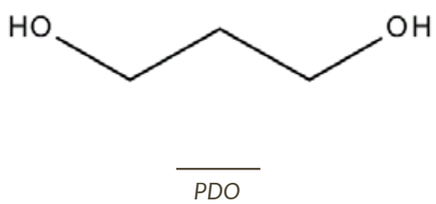
Plastics

Biodegradable plastics have drawn increasing attention in recent years. After 20 years of rigorous research, Metabolix has now successfully commercialized its microbial fermentation process. The process efficiently transforms natural sugars into biodegradable plastic (PHA - polyhydroxyalkanoates), which are marketed as Mirel Bioplastics. As of 2014, the company is producing 50,000 pounds of PHA biopolymer per month at a contracted pilot manufacturing facility and plans to continue to develop its capabilities for expansion. Development and optimization of robust industrial strains to perform this conversion has only been possible due to tools such as DNA sequencing, the synthetic construction of genes and metabolic pathway engineering.



PHA

Another noteworthy industrial breakthrough was a joint venture between industry giants Du-Pont and Tate & Lyle in 2004 for production of the multi-purpose monomer 1,3-Propanediol (PDO) from corn sugar. The global 1,3 PDO market is estimated to grow from $310 million in 2014 to $620 million by 2021. It has wide applications in cosmetics, personal care and home-cleaning products. A thorough life cycle analysis shows that the production of Bio-PDO consumes 40 percent less energy and reduces greenhouse gas emissions by more than 40 percent when compared to PDO produced via the petrochemical route. The project earned the US Presidential Green Chemistry Challenge Award in 2003. Du-Pont/Tate & Lyle expanded their plant capacity by 35 percent in 2011 and they are now a key player in the US 1,3 PDO market. With the latest partnering of METabolic EXplorer (METEX, France) and SK Chemicals (South Korea) to manufacture and market Bio-PDO, this technology will now see expansion in Asia as well.



PDO

The commercial success of the bio-based production of chemicals can be rightly attributed to investment in developing proprietary microorganisms that efficiently convert renewable sugars into these chemicals. Many other commonly used chemicals such as succinic acid, adipic acid and lactic acid can now be produced from renewable feedstocks. This capability is a direct result of the application of synthetic biology principles to constructing suitable microbes to perform the bio-transformations key to these environmentally friendly processes.

Synthetic Biology will continue to play an integral part in meeting the three major challenges faced by biofuel and biochemical production processes; (1), that of scaling production up to industrial levels, (2) increasing conversion efficiencies and (3) making the business model economically viable while remaining environmentally sustainable.

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Interview with Dr. Aparna Nagarajan,

Post Doctoral Scientist in Dr. Himadri Pakrasi's laboratory, Washington University St. Louis.

Tell me about yourself, and how you got interested in this field.

I am a postdoctoral associate in the Department of Biology at Washington University St. Louis. My first experience in synthetic biology was as a graduate student at Oklahoma State University when we synthesized parts of genes and fused them together in-silico and expressed them in cyanobacteria. We used this approach because the traditional method of cloning was toxic to cells. To me the idea of constructing a gene in a tube that functions exactly like the natural gene in the bacteria was exciting. As a post doc I have taken up other synthetic biology projects, particularly involving the integration of synthetic proteins with natural systems in cyanobacteria. The idea is to create biohybrid systems that are built upon what nature has already provided us. What got me most interested is that researchers can cleverly design their systems by combining the genetic parts as needed for their applications, almost like playing lego but with genetic parts.

If you had to sell the concept of SynBio how would you do it? Perhaps, describe it to a non-technological audience with high investment potential.

Yes, I would definitely sell the concept of synthetic biology and I feel it is more applicable in today's world especially with all the technological advancements. This is a perfect interplay of multidisciplinary efforts towards addressing current problems in science. Biological systems are very complex and often involve several interconnecting networks. To be able to isolate each of those networks without affecting others is an extremely challenging process. With synthetic biology you can design and build individual networks by taking modules from different sources, ultimately connecting them together to form a single system. In a biological sense, you can essentially combine genetic parts from various different sources, put them together into an integrated circuit and each of these components can be tuned to modulate its function. These designed circuits can then be introduced into production vehicles (bacteria) for use in a wide range of applications, from cosmetics or high value products to biofuels. Some examples could be to produce antioxidants or food flavors in the lab by cutting the intensive process of isolation and purification of these compounds.

As a field, what do you think are the implications of synbio?

Synthetic biology is used for a wide array of applications, like I mentioned earlier some of these avenues include cosmetics, antioxidants, high-value products and biofuels. Some examples include production of anthocyanin, which is an antioxidant in E. coli; this has been developed by a Mattheos Koffas from Rensselaer Polytechnic; Production of bioisoprene important for making rubber is an effort being pursued by DuPont etc.

How would you respond to consumer skepticism?

Consumer skepticism is something that exists for every field and it is good to be a little skeptical. The idea of producing useful compounds in bacteria might be daunting to consumers. However, we must bear in mind that antibiotics are obtained from various microorganisms as well. Synthetic biology has tremendous potential that can be used or misused but the key is to research responsibly and often biotech companies that do end up commercializing products work very closely with regulatory agencies to ensure all the appropriate practices are followed.

Algae and Cyanobacteria are both candidates for "biofuels and biochemicals" production, so what made you focus your research completely on Cyanobacteria? What are the potential advantages of Cyanobacteria over algae?

One prominent advantage of cyanobacteria over algae is that cyanobacteria are unicellular organisms and much easier to be engineered. Algae are eukaryotic and often strain improvement is a challenge. Cyanobacteria are more efficient in light capture and energy efficiency.

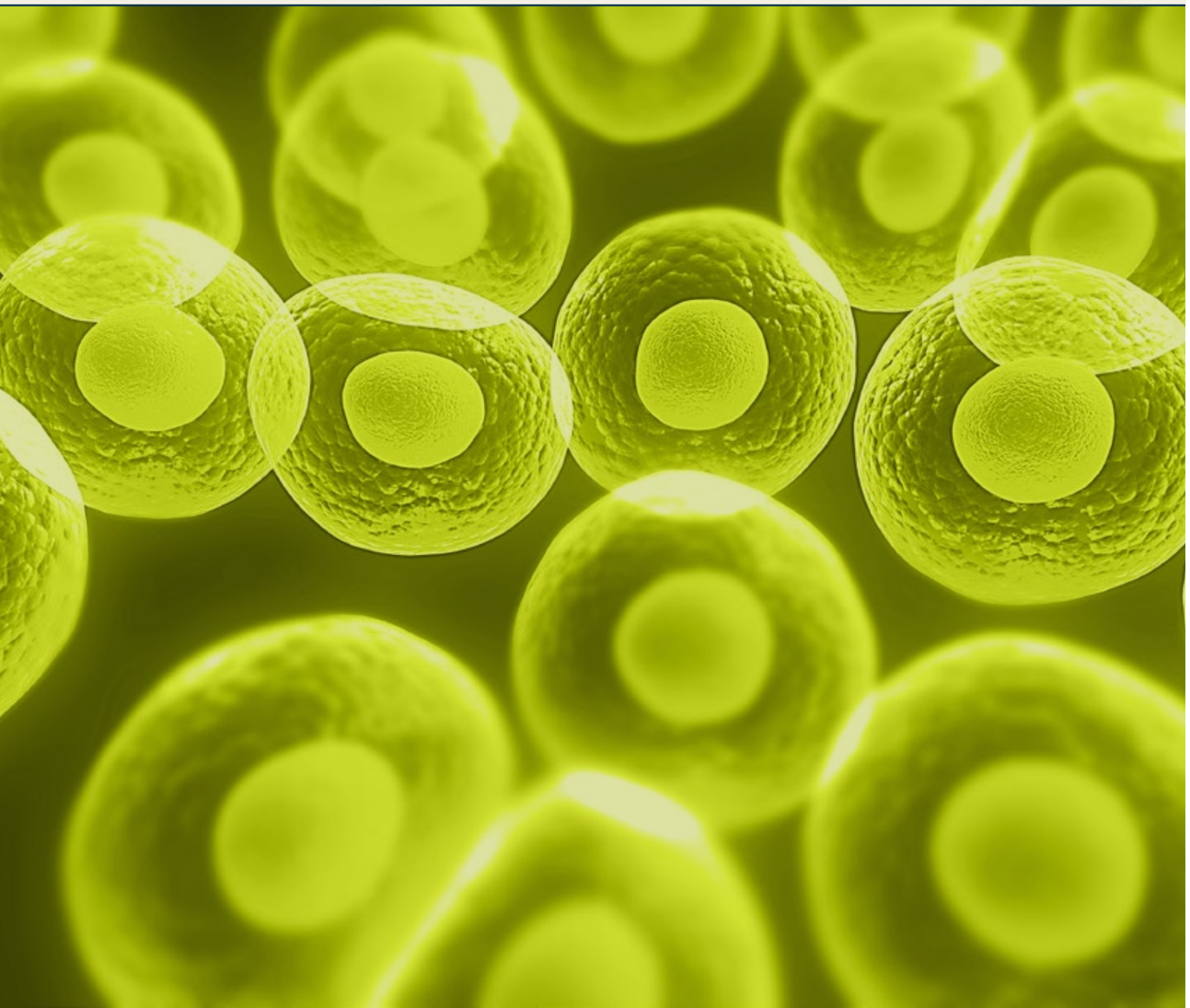
Considering synthetic biology is at the core of realizing the commercial potential of using microbes for fuel, chemical and drug production, what would be your suggestions for budding entrepreneurs in this sector? Or even for established companies who want to venture into this sector?

A lot of suggestions are probably already being administered in research labs, and synthetic biology seems to no longer be limited with the field of application. E. coli is the most chosen organism for synthetic biology but being someone who has had lots of experience with cyanobacteria, I would say that these organisms have a much greater potential for high value chemicals, fatty acids and 3rd generation fuels. These are very amenable for design and engineering and should be encouraged in synthetic biology research.

How far are we from making biofuel production from algae and cyanobacteria industrially relevant in terms of production scale, and also cost competitive compared to conventional fuels?

Biofuels from algae and cyanobacteria fall under the 3rd generation biofuels category. This has received much more attention in the last few years. There are some companies that have made sales of algal biofuels like Solazyme and Propel fuels and Sapphire energy for commercial purposes. Algenol has also made huge progress into commercializing algal biofuels. I believe the transportation industry still relies hugely on fossil fuels and there is still lot of research that needs to be done in algal biofuels to make it more consumer friendly and cost effective.

SYNTHETIC BIOLOGY AND BIOREMEDIATION



Synthetic biology has wide ranging applications in the fields of fuel and chemicals, as well as food and pharmaceuticals. However another area where it has tremendous potential for future application is in ***bioremediation***. According to the EPA, bioremediation is a treatment that uses naturally occurring organisms to break down hazardous substances into less toxic or non-toxic substances. Bioremediation has the potential to become an increasingly important waste management technique considering the environmental and economic damage caused by disasters such as oil-spills, nuclear leakage and the release of harmful pollutants into soil and water through industrial activity.

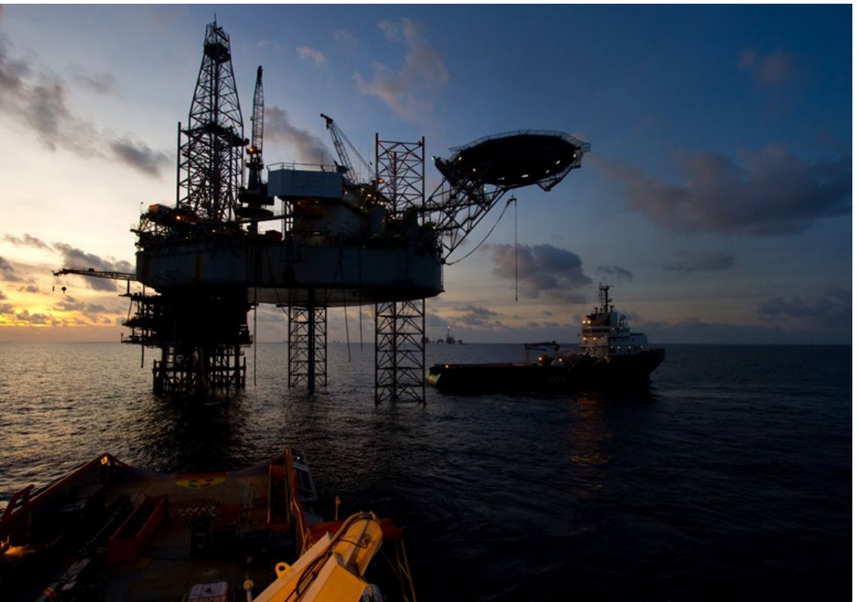
Organisms that degrade heavy metals and crude oil have been discovered to exist naturally in the environment. These oil degrading indigenous microorganisms (eg. *Rhodococcus* and *Pseudomonas bacteria*) played a significant role in reducing the overall impact of the devastating spills of the *Exxon Valdez* in 1989 and BP's *Deepwater Horizon* in 2010. Exxon spent roughly $4 billion to clean up the site and pay fines, while BP had incurred spill related expenses worth $37 billion as of March, 2012.

These organisms work together as a community to decompose oil. No single microbe, no matter how genetically enhanced, has proven better than this natural defense to date. Petroleum is a complex mixture of compounds and the communities that feed on it are equally so. A superbug fails when it competes with this community, already adapted to the environment, says microbiologist Ronald Atlas, of the University of Louisville. Atlas evaluated genetically engineered microbes and other cleanup ideas in the wake of the Exxon-Valdez oil spill in Alaska. He also notes that the natural process is rather slow, especially in areas of high oil concentration. Therefore, the current know-how gives us a great foundation to promote future synthetic biology research in this area, where blends of robust industrial strains for the quick and inexpensive destruction of these pollutants need to be developed.

Synthetic biology might offer new opportunities, he adds, but scientists need to explore how degradation pathways, developed mainly in *Escherichia coli* research, will work in other microbes better suited to survival in polluted sites. A leading scientist in this area, Victor de Lorenzo, head of the Laboratory of Environmental Molecular Microbiology at Spain's National Center for Biotechnology, uses robust microbes that can survive in harsh conditions. For instance, the soil bacterium *Pseudomonas putida* is genetically altered by replacing nonessential genes with engineered metabolic and regulatory circuits that degrade target compounds. This new genetic hard-wiring directs microbes away from easy carbon sources such as glucose and towards more challenging food sources such as industrial chemicals.

Using engineered microbes to degrade more recalcitrant chemicals such as dioxins, pesticides, and even radioactive compounds could save the millions of dollars currently spent on excavating and trucking polluted soils to hazardous waste landfills, according to Gary Sayler, Director of the Center for Environmental Biotechnology at the University of Tennessee in Knoxville. But he also says that research in this area has been under development for more than 2 decades and has yet to get out of the laboratory. The delay is due to concerns over releasing engineered microbes openly in the environment and the subjection of these organisms to extensive risk-assessment protocols by the U.S. Environmental Protection Agency (EPA)

Growing populations have made access to clean drinking water a major problem in various parts of the world and will continue to do so for years to come. Both established multinationals and start-up companies are looking at innovative ways to tackle this problem. Synthetic Genomics Inc. (SGI), a California based company, has a division named *Aquacela* that is focused on developing and harnessing microbial fuel cell technology to clean water and generate electricity. The company has conducted several successful test programs on a variety of waste water streams, including brewery waste and waste water from a sanitation plant, and is now looking for partners to commercialize its technology. Another noteworthy example would be The Synthetic Biology Institute at the University of California, Berkeley. which is currently performing cutting edge research in this area with funding support from Agilent Technologies. Its ''Environment and Agriculture'' division is developing new genetically engineered microbes that can be used to clean up water, soil and air.



Besides bioremediation applications, academic research has identified the following three areas where synthetic biology could successfully be applied:

1. Biosensors to detect pathogenic biofilms and thereby control hospital-acquired infections.
2. Enhanced mineral recovery in biomining processes, beyond the yields and productivities observed with naturally occurring microbial consortia.
3. Biosensors to detect the presence of heavy metals such as arsenic in drinking water.

The ability to design and manipulate microorganisms is a very powerful tool. Applied well it can be effectively used to sustainably solve many of the most critical challenges the world is facing today. While the production of fuels, chemicals, pharmaceuticals and food additives using synthetically engineered microbes has seen its fair share of government and private funding, as well as commercial success, large scale use of this technology is currently rather limited in areas of bioremediation, biomining and biosensors. Still, it has great potential in the years to come, provided it is properly explored.

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SYNTHETIC BIOLOGY:
Bridging the Gap Between Academia and Industry

CASE 1: The case of “creative capitalism”

Artemisinin, the antimalarial drug discovered by Amyris Biotech, is Synbio's favorite “poster child” (as noted by the ETC Group, a well-known technology watchdog) in the pharmaceutical industry. It is atypical for its mixture of lavish philanthropy from industrial donators and ad hoc institutional arrangements. The collaboration began around 2000, with the research of Jay Keasling and his team at the University of California Berkeley. They were trying to find ways to reengineer microbes into tiny cell factories for the synthetic production of organic compounds belonging to the class of isoprenoids. It so happened that a graduate student found out by chance that amorphadiene (a chemical precursor of artemisinin) also belongs to the isoprenoid class. As they were trying to provide a “proof of principle” for the new techniques of metabolic engineering, Keasling and his co-workers decided to focus their efforts on this particular substance, as it was of medical importance (Specter 2009). At the time artemisinin, the main ingredient of combination therapies against malaria, could only be obtained from sweet wormwood (Artemisia annua), a plant grown by farmers in Asia and Africa. Its supply was far short of what was required to meet world demand at prices affordable to the hundreds of millions of poor people who needed antimalarial treatments. In 2003 Keasling and his team reached a first milestone in their project. They had succeeded in building entirely new metabolic pathways for the production of amorphadiene and other isoprenoids into E. coli bacteria. The group later switched to strains of yeast (S. cerevisiae),

which could be better reengineered towards higher yields. With this new success, Keasling looked for financial support from the business world. He asked the Bill and Melinda Gates Foundation, a philanthropic organization active in the field of global health and with a special interest in malaria (Hamm 2009). The Gates Foundation was willing to fund the Artemisinin Project and made arrangements among various parties to expedite its progress. In 2004 the Foundation provided a grant of US $42.6 million to the San Francisco based Institute of One World Health (IOWH), the first non-profit pharmaceutical company in the US, and established a three-way partnership which included UC Berkeley and Amyris Biotechnologies, a spin-off biotech startup founded by Keasling and his co-workers. UC Berkeley would issue a royalty-free license to both the IOWH and Amyris to develop the technology.

A patent on the biosynthesis of amorphadiene, US7192751, was issued on 20 March 2007 and assigned to the Regents of the University of California. In exchange, Amyris would produce the drugs at cost, while IOWH would clear regulatory hurdles and oversee commercial development (IOWH press release, December 14, 2004). At the end of 2005 Keasling and his team met the next technical milestone by proving that the biosynthetic method of producing amorphadiene in reengineered yeast strains can be achieved at the laboratory scale. The biggest remaining challenge was for Amyris to increase yields several hundred fold and scale up the process to an industrial level. In 2008 IOWH decided to team up with the French pharmaceutical company Sanofi-Aventis, for the commercial development of artemisinin. Market introduction occurred in 2013. Starting in August 2014 more than 1.7 million treatments of Sanofi's ArteSunate AmodiaQuine Winthrop® (ASAQ Winthrop, fixed dose artemisinin-based combination therapy), manufactured with semisynthetic artesunate in Morocco, were shipped from Sanofi's distribution center to Burkina Faso, Burundi, Democratic Republic of the Congo, Liberia, Niger, and Nigeria.

This public-private partnership of the Artimisinin Project appears to be a perfect example of Bill Gates's concept of "creative capitalism,"hdescribed in his famous speech at the 2008 World Economic Forum in Davos, Switzerland. The challenge he pointed out was to design a system where market incentives would drive companies and scientists to do more for the poor:

"I like to call this idea creative capitalism, an approach where governments, businesses, and nonprofits work together to stretch the reach of market forces so that more people can make a profit, or gain recognition, doing work that eases the world's inequities".

Gates was however well aware that the global economic system increases the disparities in wealth.

"The great advances in the world have often aggravated the inequities in the world. The least needy see the most improvement, and the most needy get the least – in particular the billion people who live on less than a dollar a day".

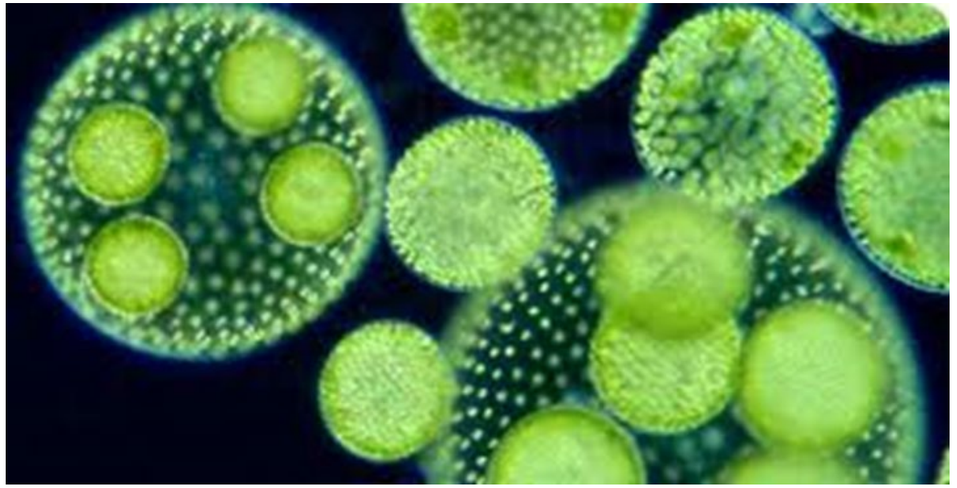
In making this connection Gates also hinted to the heavily skewed research distribution in global pharmaceutical innovation:

"Diseases like malaria that kill over a million people a year get far less attention than drugs to help with baldness".

You can read more about this technology on pg (insert pg number for 1.3.3 Case 3: Artemisinin)

CASE 2: The case of "Mr. Algae"

Dr. Mayfield's lab at the University of California San Diego develops genetic tools and investigates algae as a platform for biofuel and therapeutic protein production. One focus of the lab is to develop antibody-based therapeutics from recombinant proteins produced from the green algae *Chlamydomonas reinhardtii*. An alternative focus is to use *C. Reinhardtii* to produce novel hydrocarbons for the production of superior biofuels.



VERDANT THERAPEUTICS

Using re-constructed strains of *C. reinhardtii* that express a number of variants of human monoclonal antibodies, the Mayfield Lab has produced several forms of an antibody to the herpes simplex virus (Mayfield et al, 2003), antibodies specific to the CD19 protein of lymphoma tumors, and antibodies to the micro-organism that causes anthrax. Verdant Therapeutics is thus the "brain child" of this particular research. Verdant has developed a platform for producing Targeted Catalytics (TCATs), a single, multi-functional protein that alters a single cellular process in a specified set of cells. This delivers pharmacologically active catalytic fragments to specific cellular compartments. Since the TCAT platform is flexible and rapid, Verdant has been able to progress multiple simultaneous Antibody-Toxin Fusion (ATF) oncology therapeutic candidates. Verdant's pipeline includes promising candidates against both liquid and solid tumors. These molecules display themselves best in class performance, offering novel modes of action and superior results vs. ADCs. Verdant's advisory board is composed of some of the most senior executives in global pharma, including: James Bristol (Global SVP of R&D, Pfizer), Dennis Fenton (COO, Amgen), David Lacey (Global SVP of R&D, Amgen), and Jason Pyle (CEO, Sapphire).

"Verdant's technology is the result of three decades of research by Stephen Mayfield, CSO, and his team at UC San Diego."

RICON PHARMA

Mayfield's technology also led to the formation of Rincon Pharmaceuticals in 2004, to pursue commercialization of the research. Its main goal was to use eukaryotic algae to produce human therapeutic proteins, specifically monoclonal antibodies. Rincon's mission is to increase the availability of protein-based therapeutics by dramatically decreasing the time and cost of developing complex recombinant proteins. Rincon Pharmaceuticals, Inc. raised around $4.7 million in financing, led by Paperboy Ventures, a Washington D.C. based private equity firm with investments in high-tech and biotech companies.

TRITON THERAPEUTICS

The Mayfield lab has also produced a number of other therapeutic proteins, including serum amyloids and human growth hormones that may be effective treatment for bacterial and viral infections of the gut. Since green algae are safe to eat, they could be used as oral supplements as well. This research led to the development first of the product PhycoShield from the biotechnology startup TRITON, founded by Dr. Mayfield. PhycoShield™ (Mammary Associated Amyloid) is a family of all natural mammalian proteins that may help in the prevention of intestinal diseases by repelling harmful infections (e.g., E. coli), combating existing infections, and improving nutrient digestion. MAA has been extensively tested over the past 20+ years. The safety and efficacy of colostrum has been tested for decades, through 33 studies conducted on over 2,750 mammalian subjects, including 1100 humans. There are few other products in the world that have such unequivocally positive effects. Hence, fractionated colostrum is an approved product by the FDA for use in treating certain digestive disorders such as ulcerative colitis. Diarrheal diseases in animals cost more than $5 billion per year globally. This raises the the cost of livestock, increasing the price to the consumer and reducing the security and safety of the food production chain. MAA has the potential to reduce diarrheal diseases worldwide, which kill approximately 20 percent of the world's livestock each year, as well as accounting for over two million human deaths, and is the leading cause of infant mortality in developing countries. Heliae, a leader in the development of advanced algae production technologies, announced a strategic partnership with Triton for the completion of its Series-A equity financing of $5 million, and has also purchased a minority share of Triton as a part of their strategic partnership.

"Triton is the result of over 20 years of academic and private sector research", said Dr. Pyle, CEO of Triton. **"Dr. Mayfield's ground-breaking research has culminated in Triton's proprietary technology for easy and rapid production of proteins that have applications in numerous markets worldwide"**

A key focus of work in the Mayfield lab is developing algal genetics and recombinant technologies. This will be essential expertise for producing algae-derived biofuels on a large scale. Molecular genetic tools have been developed for only a few algae, which include the green algae Chlamydomonas reinhardtii, and the diatoms Phaeodactylum tricornutum and Thalassiosira pseudonana. They have shown that C. reinhardtii can be engineered to produce novel hydrocarbon molecules that are superior biofuels, demonstrating the potential of microalgae as a biofuel source. Molecular genetic tools are being developed that will allow for robust recombinant protein expression in algae, reengineering algae towards the production of biofuel molecules.

This has led to the formation of one of the most successful startups — Sapphire. At Sapphire they have developed a technology platform that uses non-potable water and non-arable land to grow algae, simultaneously capturing CO2 in open ponds and providing renewable solutions to the biofuel problem. With more than 300 issued and pending patents across the technological spectrum, Sapphire does research on subjects that encompass the full value chain of producing algae on a large scale—from strain development to cultivation, harvest and conversion. Sapphire is the first—and only—company to produce a renewable source of crude oil continuously from algae biomass, operating the largest algae-to-energy facility in the world.

Sapphire Energy is backed by a team of the nation's leading researchers and supported by long-term investors such as The Wellcome Trust, ARCH Venture Partners, the Rockefeller family's Venrock, Bill Gates' Cascade Investment, and the agriculture industry giant Monsanto. It has cultivated research and engineering partnerships with the Linde Group, Earthrise Nutritionals, Monsanto, and the Institute for Systems Biology, in addition to business agreements with Tesoro Refining and Marketing, Phillips 66, and Sinopec.

In 2009, Sapphire received $100 million Series B funding from venture capitalists Arch Venture Partners, the Wellcome Trust, Venrock, and Cascade Investment, which is Bill Gates' investment arm in Kirkland, WA. The company built a 70,000-square-foot lab in San Diego and a 22-acre farm in New Mexico. Its algae-derived fuel has successfully powered cars and jets. Impressed, Exxon Mobil threw $600 million into algae oil research. Since then it has secured more funding from many other companies. Series C investment funding included Arrowpoint Partners, Monsanto and other undisclosed investors. With this varied investment behind it, Sapphire Energy's total funding from private and public sources substantially exceeds $300 million.

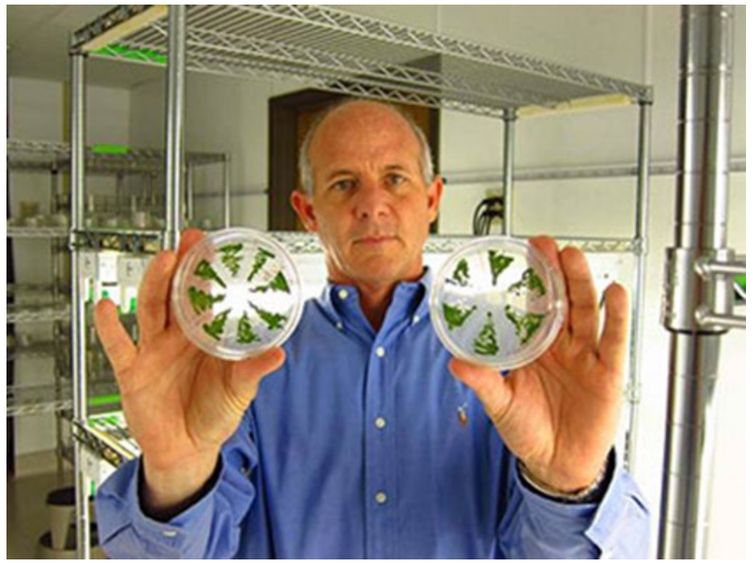
Perhaps with all this in mind, Sapphire was named one of the 50 Hottest Companies in Bioenergy for 2014-2015.

At the 2014 Algae Biomass Summit Mayfield optimistically commented,

"We're right on the edge now", which is "where people are making products and getting ready to sell them."

In the last month, eight major companies have consulted with Mayfield about product development.

All told, Steven Mayfield was probably not too surprised when in December, he got a call from the Office of Science and Technology (at the White House), looking for advice on food security and saying, "We hear you're Mr. Algae."



CASE 3: The case of “Making the Impossible Possible”

Reports from the Sustainable Development Solutions Network claim that the demand for food will greatly increase owing to rising incomes and increasing population. FAO predicts that the world population will be around 9 billion in 2050, and feeding new inhabitants will require raising overall food production by at least 70 percent. Contemporary food habits have already exerted extreme pressure on terrestrial and aquatic ecosystems, and they fail to provide adequate nutrition. While 870 million people suffer from insufficient calorific intake today, and a billion or more from micronutrient deficiencies, there is another 1.4 billion who suffer from being overweight or obesity.

Patrick O. Brown, a Stanford University professor, recently founded the start-up “Impossible Foods” which has been named as one of CNBC's 2015 Disruptor 50 companies. He told the Wall Street Journal, “Livestock is an antiquated technology.”

Impossible Foods is making meats and cheese from plants, using a bioengineered product from plant substrates. They have even incorporated a molecule heme, extracted from the roots of legumes, which is a replica of hemoglobin (what they call “plant blood”), which makes the “meat bleed”. They use decades of experience in the gene expression patterns of the yeast and human genomes, their organization, and physiological logic to take proteins and nutrients from greens, seeds and grains and recreate the texture and the taste of meat and diary products. With meat created from plants, there is no concerns about cholesterol, hormones, antibiotics or the chance of being contaminated by bacteria in a slaughterhouse. They claim that the company will be able to make any of the foods currently derived from animals—today’s cheese, milk, bacon, pork, steak and chicken—directly from plants.

Impossible Foods have already received financial support to the tune of $74 million since it was started in 2012 from Khosla Ventures, Horizons Ventures and Bill Gates.

"Raising meat takes a great deal of land and water and has a substantial environmental impact," Gates wrote on his personal blog, Gatesnotes.com. *"Put simply, there's no way to produce enough meat for 9 billion people. Yet we can't ask everyone to become vegetarians. That's why we need more options for producing meat without depleting our resources."*

The company is planning to launch their product in 2016, and Brown, whose team of scientists chefs, farmers and engineers started modifying the ingredients a year and a half ago, said,

“The Burger gets better every week”

They have conducted many taste tests of prototypes and he commented that

“We're at a point where it doesn't matter if you're a contractor or a chef. If you aren't told that it is anything other than ground beef, you'll assume it is. We now have to produce a consistently great product at scale."

Right now they spend around $20 producing each hamburger patty, and they have to come up with a way of decreasing the cost and develop marketing plans for the launch. Brown cited research which said

“If an alternative could satisfy them, provide all the pleasure they get from eating meat but was made from plants, they would prefer it."

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Gurshagan Kandhola's research focuses on production of biofuels and bioproducts from cellulosic biomass and purification of bioactive molecules from natural extracts using Centrifugal Partition Chromatography. She has done her BS in Biotechnology Engineering from Panjab University, India and MS in Food and Bioprocess Engineering from University of Illinois, Urbana-Champaign. She is currently a PhD candidate in Biological Engineering at the University of Arkansas, Fayetteville.

Tuseeta Banerjee's research focuses on developing robust algorithms to study the dynamics of a small quantum system in a protein or chromophore backbone. She has developed a more realistic picture to model the quantum mechanical interaction in a redox reaction or a proton transfer reaction, and plans to use it to study such reactions in enzymatic complexes or photosynthetic reaction centers. She is currently a PhD candidate and a Graduate Fellow in the Department of Chemisty, University of Illinois Urbana Champaign. She has received her Bachelor's with Honors from St. Xavier's College, Kolkata, India and Master's in Chemistry, Indian Institute of Technology Bombay, India, ranking first in her class.

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