Synthetic Biology, Biodiversity & Farmers

Case Studies by ETC Group

The Synthetic Biology industry has had trouble scaling up its biofuel production, and is shifting focus away from biofuels to high-value, low-volume products. The industry's main target is compounds found in plants (e.g. essential oils, flavours, fragrances, colourants and pharmaceuticals), which are traditionally cultivated by farming communities in the global South.

The SynBio industry is moving in on spices and other high-value, low-volume commodities. *Frank Kovalchek*

In this report, ETC Group presents a series of case studies outlining some specific ways that livelihoods from traditional agricultural production may be adversely affected as synthetic biology-based substitutes for high-value commodities enter the market over the next few years. The engineering and patenting of metabolic pathways that could apply to a wide range of natural products is also a concern.

METABOLIC PATHWAYS: Synthetic biology companies are engineering "metabolic pathways" in microbes to act as "biological factories" that produce desired compounds. According to current scientific understanding, as few as eight key pathways may be responsible for almost all of the 200,000 known natural plant compounds. Synthetic biologists are rapidly decoding, re-constructing and patenting these pathways. In the words of synthetic biologist Jay Keasling: "We ought to be able to make any compound produced by a plant inside a microbe."[1]

> **"We ought to be able to make any compound produced by a plant inside a microbe."**

IMPACT: If commercially viable, synthetic biology's patented organisms have the potential to destabilize natural product markets, disrupt trade and eliminate jobs and livelihoods. New, bio-based substitutes deemed "equivalent" to natural products could have far-reaching impacts on agricultural economies, especially for those producers without the information or resources to respond to sudden shifts in natural resource supply chains. Earlier efforts to use new technologies (e.g., plant cell culture and transgenics) to manufacture high-value natural products were largely unsuccessful. It is not known how well compounds produced through synthetic biology will compete in the marketplace with botanically-derived products; likewise, knowing precisely which products, which small farmers and whose economies will be most affected and how quickly is difficult, but some of the earliest impacts may be seen for growers of Artemesia annua, Coconut, Vanilla, Vetiver, Star Anise and Saffron, affecting livelihoods and associated traditional knowledge.

PLAYERS: The global market for plant-derived compounds has been estimated at $65 billion. The market for flavour and fragrance compounds alone is over $20 billion p/a (per annum). The natural fatty acids market alone was valued at $7.2 billion in 2011. It is conservatively estimated that at least 50% of pharmaceutical compounds on the market come from plants, animals and microorganisms. The world's largest corporations are beginning to turn to synthetic biology for supplies of cheaper, more easily accessible high-value compounds traditionally sourced from plants. The Synthetic Biology market is predicted to be worth almost $40 billion by 2020.

PRODUCTS AFFECTED: Some biosynthesized compounds have already come to market and many others are in the pipeline. Among the near-term targets:

• Isoprene rubber: Could affect supply chain for both natural and synthetic rubber. The livelihoods of 20 million small holder families, mostly in Asia, depend on natural rubber. (The market for isoprene is $2 billion p/a).

• Coconut Oil: Natural fatty acids derived from coconut and palm kernel oil are a staple of the multibillion-dollar oleochemcial industry, supporting livelihoods of over 25 million people in the Philippines.

• Artemisia: previously sourced from over 100,000 Asian and African farmers (~$90 million market p/a). The recent introduction of SynBio artemisinin has already rapidly decreased the botanical production of this important drug.

• Saffron: Iran produces an estimated 90% of the world's saffron, with export markets in over 40 countries ($660 million market p/a).

• Vanillin: An estimated 200,000 people worldwide are involved in the production of cured vanilla beans ($240 million market p/a).

• Vetiver Oil: In Haiti alone, 60,000 people depend on vetiver production ($10 million market p/a).

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1. Jay Keasling, quoted in Michael Specter, "A Life of its Own: Where will synthetic biology lead us?," The New Yorker, 28 September 2009, p. 59.

For More Information

ETC Group has published several documents explaining and analyzing the impact of Synthetic Biology on biodiversity and livelihoods including *Extreme Genetic Engineering - An introduction to Synthetic Biology*, *The New Biomassters - Synthetic Biology and the Next Assault on Biodiversity and Livelihoods* and *The Principles for the Oversight of Synthetic Biology* available on our website: www.etcgroup.org/en/issues/synthetic_biology

The Potential Impacts of Synthetic Biology on the Conservation & Sustainable Use of Biodiversity: A Submission to the Convention on Biological Diversity's Subsidiary Body on Scientific, Technical & Technological Advice (A Submission from Civil Society)
www.etcgroup.org/en/node/5291

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To obtain any missing references, please email *info@etcgroup.org*

Artemisinin

A SynBio Case Study

About 100,000 farmers currently grow *Artemisia annua*. *Novartis AG*

Product: Artemisinin, the key ingredient in the world's most effective anti-malarial drug, is extracted from Artemisia annua, an ancient medicinal plant commonly known as sweet wormwood. Artemisinin is incorporated into WHO-authorized antimalarial cocktail drugs called ACTS (Artemisinin Combination Therapies).

Status: Supported by funds from the US Gates Foundation, Synthetic biologists at California-based Amyris, Inc. engineered yeast to produce artemisinic acid, a precursor to artemisinin. Pharmaceutical giant Sanofi Aventis has now scaled up commercial production of between 35-60 MT of what is marketed as Semi-Synthetic Artemisinin (SSA). Amyris founder Jay Keasling has indicated interest in having SSA take over full global production.

Affected Country/Region: Until 2013 natural artemisinin was sourced entirely from an estimated 100,000 small farmers in Asia and Africa, as well as wild harvesters of the crop in China. Currently 80% of all artemisinin derived from Artemisia crops is produced in China. Vietnam is a distant second (around 10%), with the remainder coming from Madagascar, Kenya, Tanzania and Uganda. A small amount is grown in India. Farmers have also been growing trial crops of Artemisia in Zimbabwe, South Africa and Nigeria. The average crop area per farmer in China and Africa is around 0.2 hectares. The introduction of SSA coincided with a dramatic fall in artemisinin prices in 2013. Subsequently 2014 plantings of Artemesia are at only a third of previous production levels and commercial operations are at a standstill.

Market: Current market demand for artemisinin is about 150-180 metric tonnes (MT). The major buyers are a handful of approved pharmaceutical companies making ACT drugs.

Commercialization: Already commercialized . In 2013 Sanofi produced 35 MT of SSA with production rising to 50-60 MT in the coming years. Although advocates claim synthetic biology will make anti-malarial drugs cheaper, in fact the current production-run of SSA is priced at between $370-$400 per kg, significantly above the price of naturally-derived artemisinin, which sells for around $250-$270 per kg. Natural artemisinin producers further charge that its impossible to know the true costs structure of SSA since it has received extensive philanthropic subsidies. As the last step before being put on the market an intermediate version of the synthetic artemisinin has been approved by the WHO for the preparation

Synthetic Biology Artemisinin Commercialisation:

- 2013 - Production goal 35 MT–for Sanofi use.
- 2014–Production capacity 50-60MT.
- Cost estimate is $350–$400/kg (not-for-profit price).

of approved artemisinin derivatives (such as artesunate).

About Artemisinin

The key ingredient in the world's most effective drug treatment for malaria–artemisinin–is extracted from an ancient medicinal plant, Artemisia annua, commonly known as sweet wormwood. According to the WHO, artemisinin-based combination therapies (ACTs) provide the most effective treatment against malaria. The pharmaceutical industry sources natural artemisinin from thousands of small farmers who grow Artemisia annua, primarily in China, Vietnam, Kenya, Tanzania, Uganda, Madagascar and India.

Origins of Semi-Synthetic Artemisinin

In 2006, Professor Jay Keasling of the University of California-Berkeley and 14 collaborators announced they had successfully engineered a yeast strain to produce artemisinic acid, a precursor to the production of artemisinin. Supported a $53.3 million grant from the Bill & Melinda Gates Foundation, the researchers achieved the complex feat of engineering the metabolic pathway, which comprised 12 new synthetic genetic parts. Inserted into yeast, the engineered pathway makes the yeast produce artemisinic acid. A chemical process is then used to convert artemisinic acid to artemisinin. In 2008, Amyris granted a royalty-free license for its synthetic yeast to Sanofi for the manufacture and commercialization of artemisinin-based drugs, with a goal of market availability by 2013. Aiming to be efficient and fast, the production of artificial Artemisinic acid is supposed to take less than three months. Sanofi built a new facility for the chemical conversion of artemisinic acid in Italy and began the world's first commercial production of synthetic microbe-derived artemisinin in April 2013.

Sanofi initially produced 35 metric tonnes (MT) in its first 2013 batch. It has indicated plans to annually produce enough semi-synthetic Artemisinin to meet between a third and a half the global demand. Sanofi says it will ensure its distribution under the "no profit, no loss" principle. The key researcher associated with the Synthetic Artemisinin project is synthetic biologist Jay Keasling, founder of Amyris and professor at the University of California at Berkeley. Sanofi's production is slated to increase to 60 MT per year. Keasling has publicly stated that the goal is now to fully replace the botanical version. Keasling is rumoured to be in discussions with other Pharmaceutical companies to provide a process for synthetic biology-derived artemisinin different than that licensed to Sanofi.

Impacts of Semi-Synthetic Artemisinin

A 2006 report from the Netherlands-based Royal Tropical Institute predicted the effects of synthetic sources of artemisinin: "pharmaceutical companies will accumulate control and power over the production process; Artemisia producers will lose a source of income; and local production, extraction and (possibly) manufacturing of ACT in regions where malaria is prevalent will shift to the main production sites of Western pharmaceutical companies."

The report warned that the prospect of synthetic artemisinin production could further destabilise a very young market for natural Artemisia, undermining the security of farmers just beginning to plant it for the first time: "Growing Artemisia plants is risky and will not be profitable for long because of the synthetic production that is expected to begin in the near future."

Fueling the Boom-bust Cycle?

According to the Royal Tropical Institute's analysis, sufficient supplies of Artemisia could be met solely by increasing cultivation of sweet wormwood.
The report estimated that between 17,000-27,000

hectares of Artemisia annua would be required to satisfy global demand for ACTs, which could be grown by farmers in suitable areas of the developing world. Indeed, subsequent to the Royal Tropical Institute's report, farmers planted tens of thousands of additional hectares and in 2007 the artemisinin market became saturated with supply.

Ton Rulkens

Prices crashed from more than $1,100 per kilogram to around $200 per kilogram driving 80 processors and many small farmers out of business. As a result, availability once again dropped below demand. Though poorly managed, the 2007 production spike demonstrated the feasibility of meeting world demand for artemisinin with botanical supplies. The international drug-purchasing facility, UNITAID, subsequently established the Assured Artemisinin Supply System (A2S2) initiative to provide loans and supply chain investment to increase the Artemisia harvest to sustainable high levels. In 2011, artemesinin production from harvested crops was estimated at between 150-170 tonnes, close to 2007 levels.

The creation of the A2S2 was largely successful in calming the swings in price and ensuring stable botanical supply to meet medicinal needs. Sanofi claimed that introducing limited amounts of synthetic biology-derived artemisin would also help calm these price spikes. However, its introduction instead appears to have been followed by increased volatility. Experts had warned that a badly-managed introduction of synthetic artemisinin could instead cause further instability and lead farmers to refrain from planting in the face of competition from synthetic microbes.

"Early on, it was not about replacing the agricultural form… and now I think it's nearly inevitable that it will shift over." – Jay Keasling

"If it's brought in too fast it could create huge shortages, because people will stop producing the natural stuff," says Malcolm Cutler, technical adviser to the Assured Artemisinin Supply System initiative, which organized the Nairobi conference.

This may be what is happening now. 2014 prices of botanical artemisinin have dropped to a decade low and plantings are down by 2/3rds. If the prices of artemisinin rise quickly again because of the reduced plantings, SSA may undercut natural production cost in some markets (eg China). Far from calming market volatility, SSA may have helped fuel it.

Natural producers fear that the competition is unfair if SSA is marketed at a "not for profit price" based on large subsidies from the Gates Foundation. They point out that the real costs of SSA have been hidden by philanthropic support.

References: For a list of sources cited in this case study, email *info@etcgroup.org*.

Cocoa Butter

A SynBio Case Study

PRODUCT: Cocoa butter, the main ingredient in chocolate, comes from cocoa beans grown by smallholder farmers in 30 tropical countries. "Cocoa butter equivalents" are composed of vegetable fats derived from a variety of plant sources.

Cacao farmer in Costa Rica *photo: Everjean*

STATUS: Solazyme, a California-based synthetic biology* company, is engineering oil-producing algae that are fueled by sugar feedstocks in giant fermentation tanks. In 2012, the company announced that it has developed a new high-value "tailored oil" with a fatty acid composition very similar to cocoa butter.[1] The company is developing the cocoa butter substitute for use in food and personal care (e.g. cosmestics, lotions) products.[2]

AFFECTED COUNTRY/REGION: Between five and six million smallholder farmers grow cocoa. West Africa accounts for over 71% of all cocoa bean production;[3] the world's top 3 cocoa bean producers–Côte d'Ivoire, Ghana and Indonesia–account for over two-thirds (68.6%) of all cocoa bean production.

MARKET: The value of the worldwide cocoa butter market is about US$6 billion.[4] The current market for *cocoa butter equivalents* is an estimated $US600 million per annum.[5]

COMMERCIALIZATION: Not known. After agreeing to provide information via telephone interview, Solazyme abruptly declined to answer further questions about its work on the development of a cocoa butter-like engineered oil and directed us to the company's website.[6]

Introduction

In late 2012, the CEO of California-based Solazyme announced that his company had developed a new high-value "tailored oil" with a fatty acid composition very similar to cocoa butter.[10] According to Solazyme: "We've also developed another first of its kind capability, the ability to control the specific position of specific fatty acids in the oil. Positioning the fatty acids plays a major role in creating the physical properties of cocoa butter like its sharp melting curve. The same melting properties of cocoa butter are ideally suited for a range of personal care products such as lotions, emollients and moisturizers."[11]

***Note:** With growing public awareness and concern about the use of synthetic biology to create synthetic food flavors/fragrances/ingredients, the synthetic biology industry is in the midst of a strategic "makeover" and is seeking to distance itself from the "synthetic biology" label. Although Solazyme now insists that it is not a synthetic biology company, it is widely identified as a synthetic biology company and has previously self-identified as such in the past. The company uses techniques such as "directed evolution"[7] and "metabolic engineering"[8] that are generally recognized as synthetic biology. Solazyme's filings with the US Securities & Exchange Commission refer to 'targeted recombinant technology.' A spokesperson for Solazyme confirms that the company is using the same technologies that it used previously when it described itself as 'synthetic biology' company.[9]

In response, one Internet pundit brashly trumpeted, “Step aside cocoa farm, synthetic biology is on its way… It isn’t unrealistic to think that the company would eventually become a major supplier of sustainable cocoa butter alternatives.”[12] Another observer speculated that Solazyme’s technology will enable the “de-regionalization” of cocoa butter production and thus eliminate constraints associated with the sourcing of natural cocoa beans from tropical countries: volatile prices, unpredictable supplies, long-distance shipping, possible geopolitical instability or variables associated with weather and crop pests.[13]

> *“Step aside, cocoa farm, synthetic biology is on its way”*

Founded in 2003, California-based Solazyme is a publicly-traded company that specializes in the development of engineered microalgae for the production of “tailored” oils for use in chemicals, foods, fuels and personal care/health products. The company boasts that its ability to tweak the molecular composition of oil-producing algae enables them to “go beyond anything that natural plant oils can do, with huge productivity and great yields.”[14]

Solazyme focuses on strains of single-cell microalgae that naturally produce oil. The company’s goal is to manipulate the cellular machinery of microalgae to produce specific kinds of lipids[15] (fatty acids) on demand, and to ramp up yields of the oil-bearing organism by feeding it sugar feedstocks (from corn or sugarcane) in industrial fermentation tanks. The company claims that it has successfully engineered microalgae to mimic the lipid (fatty acid) profile of naturally occurring oils such as cocoa butter.

Solazyme’s financial outlook appears shaky–the company is more than $300 million in debt and has few product revenues to date. However the company has achieved commercial-scale production of several tailored oil products, and is partnering with high-profile, heavyweight corporations, including Unilever, Bunge, Dow, Archer Daniels Midland (ADM), Mitsui & Co and AkzoNobel, among others. Solazyme holds 20 issued US patents, six issued foreign patents and over 175 pending patent applications filed in the US and other jurisdictions.[16] In January 2014, Solazyme announced that it is producing commercial supplies of tailored oils at ADM’s facility in Clinton, Iowa and another facility operated by American Natural Products in Galva, Iowa.[17] In March 2014, Solazyme launched a new product line: “Encapso,” an encapsulated lubricant for oil drilling and hydraulic fracturing (fracking).[18] In May 2014 Unilever announced that it is using Solazyme’s “Algal Oils” in the production of Lux brand soap.[19] Since 2011, Solazyme has sold microalgae-derived ingredients for the company’s commercial skin care products known as “Algenist.” Solazyme has a joint venture with agribusiness giant Bunge to build and operate a commercial-scale tailored oils production facility next to Bunge’s Moema sugarcane mill in Brazil.

Background: Cocoa Production

Some 5-6 million farmers grow cocoa in hot, rainy and tropical areas of Africa, Asia and Latin America across a narrow belt within 10-20 degrees latitude of the Equator. An estimated 40-50 million people depend on cocoa for their livelihood.[20]

Cocoa is grown by farmers in more than 30 tropical countries.[21] **Smallholder farmers account for 80-90% of world cocoa production.** In Africa and Asia, a typical cocoa farm covers 2-4 hectares (4.9 -12.3 acres).[22]

The International Cocoa Organization (ICCO) forecasts that in 2013/14, West African producers will account for 72% of global cocoa bean production, followed by cocoa farmers in the Americas (16%) and Asia and Oceania (12%).

Like most tropical agricultural export commodities, cocoa is subject to boom and bust cycles. For example, cocoa prices plunged to a 27-year low of $714 per tonne in November 2000, and soared to a 32-year high of $3,775 per tonne in March 2011.[25] (With demand for cocoa currently exceeding supply, cocoa prices are rising. In March 2014 cocoa prices reached US$3,031 per tonne in New York and £1,896 per tonne in London). Volatility in cocoa prices is due to many factors, including: extreme weather and climate change, pests and disease, political instability

Cocoa beans. *photo: Everjean*

in producing countries and corporate concentration in the cocoa value chain.

Cocoa Market Concentration

The huge number of farm families in the tropics who make their living growing cocoa stands in stark contrast to the increasingly consolidated control of industrial cocoa bean buyers and traders. The corporations that control the cocoa market are among the most powerful agro-industrial commodity trading firms in the world. **Today, just three global cocoa bean traders/processors** (Barry Callebaut–26%; Cargill–21%; ADM–17%)**, account for an estimated 64% of the world's cocoa grindings.** (Based on global production of about 4.4 million tonnes.)[26]

In late 2013, Cargill was on the verge of acquiring ADM's global cocoa & chocolate operations[27], a deal that would have allowed just two firms to dominate the global market. The cocoa merger talks melted, however, and in April 2014 ADM announced that it would retain its cocoa buying/processing operations and sell its chocolate business.[28] However, ADM's current partnership with Solazyme does not involve cocoa or cocoa butter equivalents.

Chocolate is big business, but small farmers who grow the main ingredient (cocoa) earn a tiny share of the estimated US$125 billion spent per annum on chocolate products. According to Fairtrade Foundation, despite rising cocoa prices, in 2010 West African growers received just 3.5% to 6% of the average retail value of a chocolate bar compared to 18% in the 1980s.[29] By contrast, the manufacturers' share shot up from 56% to 70% and the retailers' from 12% to 17% over the same period.[30]

The global appetite for chocolate is huge, and the demand for cocoa butter (the main ingredient in chocolate) is growing, particularly in Asia. The vast majority of cocoa butter is used for confectionary (i.e. food) and drink products. The proportion of cocoa butter that is used for *non-edible* uses (i.e. personal care products such as cosmetics, lotions) is very small: only 1-2% of total production, and it depends largely on the price of cocoa butter.[31]

Is there a market for a cocoa-butter-equivalent derived from engineered algae?

Solazyme's quest to develop a cocoa-butter-like engineered algal oil will face steep competition from an established industry that already produces cocoa butter alternatives. The current market for **Cocoa Butter Equivalents (CBE)**[34] is in the neighborhood of US$600 million per annum; the CBE market varies from year to year depending on the price of cocoa butter, sometimes by 30% or more.[35] In the EU, for example, CBEs are sourced from cheaper plant-

- **West Africa accounts for over 71% of all cocoa bean production worldwide.**[23]
- **The world's top 3 cocoa bean producing countries, Côte d'Ivoire, Ghana and Indonesia accounted for over two-thirds (68.6%) of all cocoa bean production in 2012/13.**[24]
- **The top 5 cocoa producing countries accounted for 80% of the world supply:**

Leading Cocoa Bean Producer Countries
(based on 2012/13 estimates)

Country	Thousands of Tonnes	% Share of World Market (estimate)
Côte d'Ivoire	1449	36.7%
Ghana	835	21.2%
Indonesia	420	10.6%
Cameroon	225	5.7%
Nigeria	225	5.7%
Top 5	3154	80%
Total World	3942	100%

Source: International Cocoa Organization (ICCO) derived vegetable fats, including: illipé (*Shorea* spp.), palm oil (*Elaeis guineensis, Elaeis olifera*), sal (*Shorea robusta*), shea (*Butyrospermum parkii*), kokum gurgi (*Garcinia indica*), and mango kernel (*Mangifera indica*). The composition and price of CBEs depends on the supply of many different plant-based oils.[36]

The CBE market is used to "stretch" the cocoa butter supply–or to provide a cheaper raw material for lower-quality chocolate or chocolate-like products. Most countries have regulations governing the definition of cocoa/chocolate products and the minimum percentage of cocoa butter that must be used. In the EU, for example, a product can't be called "chocolate" if the end product is made up of more than 5% vegetable fats other than cocoa butter; the labeling of chocolate products containing vegetable fats other than cocoa butter must bear the statement "contains vegetable fat in addition to cocoa butter."[37]

- **The value of the world-wide cocoa butter market is about US$6 billion.[32]**
- **The amount spent world-wide on retail purchases of chocolate products is in the neighborhood of US$125 billion.[33]**
- **The current market for cocoa butter equivalents is an estimated $US600 million per annum.**

Conclusion

The potential of a biosynthesized cocoa butter alternative derived from modified algae does not currently threaten the livelihoods of smallholder farmers who grow naturally-sourced cocoa beans. However, if Solazyme is able to achieve low-cost, high-yielding customized oils and fats, the company could displace or disrupt markets for some tropical oils (such as coconut oil, palm oil, palm kernel oil, shea butter) that are typically used in cocoa butter equivalents.

Even if Solazyme is able to scale up production of modified algal oil to mimic cocoa butter-like properties, the end product must compete with cheaper sources of plant-derived vegetable fats that are currently used for cocoa butter equivalents. To date, the company has not announced a corporate partner to support the development of a cocoa butter alternative. Although Solazyme claims that its process is "sustainable", the company's large-scale fermentation process depends on access to large quantities of sugar feedstocks (maize or sugarcane). Solazyme has noted that prices of sugar feedstocks are volatile and supplies are not dependable.[38]

Some observers note that Solazyme's engineered oil with cocoa-butter-like properties may be the answer to the current under-supply of cocoa on the world market. Although demand for cocoa beans currently outpaces supply, the boom and bust cycle in world cocoa markets is nothing new. Corporate cocoa giants are currently investing millions of dollars in new cocoa grinding operations and processing facilities. For example, with demand for chocolate surging in Asia, Indonesia expects to triple output of cocoa beans by 2020 and cocoa grinding capacity there is forecast to jump 85% by the end of 2014.[39] It is unlikely that corporate cocoa barons would be investing millions in expanded cocoa grinding/processing capacity if a cheaper, biosynthesized cocoa butter was capable of displacing naturally-derived cocoa butter.

Finally, public resistance to synthetic biology's engineered foods is real and growing. A recent survey of public attitudes about synthetic biology indicates that one of the applications of synthetic biology that generates "a lot of criticism and concern" for consumers is the development of synthetic flavors to replace natural flavors and ingredients such as vanilla and citrus in foods that are intended for human consumption. According to the researchers: "The discussions reveal that participants are not so much concerned about developing synthetic ingredients for paint as they are about developing synthetic food additives that humans would ingest.[40] When it comes to vanilla, there is a sense that we have what we need and so a synthetic version is not needed–it would create a potential risk for no good reason."[41]

If the public is concerned about SynBio's vanilla substitute, the notion of bio-synthesized cocoa would be equally unappetizing to chocolate lovers worldwide. The corporate cocoa barons won't need a public relations firm to figure that out.

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7 'Directed Evolution' attempts to rapidly 'evolve' novel DNA sequences or expressed proteins either in the lab or in a computer towards a particular outcome. Typically, directed evolution involves selecting an existing genetic sequence and creating an array of mutations which are then introduced into a model organism and screened for a specific outcome (e.g. production of a chemical or improved photosynthesis).

8 Metabolic engineering refers to the altering of several interacting genes or the introduction of new metabolic pathways within a cell or microorganism to direct the production of a specific substance, including the synthesis of natural products (pharmaceutical ingredients, flavours, fragrances, oils, etc.) as well as high-value chemicals, plastics and fuels.

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33 Ibid. According to Haws: This excludes the amount spent on products flavored with cocoa powder, such as ice cream, cookies, etc.

34 According to the International Organization for Standardization (ISO) "cocoa butter equivalents" is the general term for fats used to replace cocoa butter in chocolate. They resemble the chemical composition and physical properties of cocoa butter very closely, making them therefore extremely difficult to quantify and even in some cases to detect. In principle, cocoa butter equivalents must by definition be fats low in lauric acid, rich in symmetrical mono-unsaturated triacylglycerols of the type 1,3-dipalmitoyl-2-oleoylglycerol, 1-palmitoyl-2-oleoyl-3-stearoylglycerol and 1,3-distearoyl-2-oleoylglycerol, miscible with cocoa butter, and obtained only by refining and fractionation. https://www.iso.org

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Coconut, palm kernel and babassu oils

A SynBio Case Study

PRODUCT: Industrially useful natural fatty acids known as "lauric oils"–capric acid, lauric acid, myristic acid, palmitic acid–are currently derived from coconut oil, palm kernel oil and also babassu seed. So too are a suite of "fatty alcohol" ingredients such as lauryl alcohol and myristyl alcohol. These are the key ingredients for common oleochemical products such as detergents, soaps and cosmetics.

A coconut palm in the Philippines. *photo: Cristian Bortes*

STATUS: Three California-based companies are now producing fatty acids and fatty alcohols using synthetic biology. Solazyme, Inc. has engineered algae to create strains whose oils are "genetically tailored" to express lauric acid, capric acid or myristic acid. Solazyme is also developing strains to produce palmitic acid and oleic acid. Codexis, Inc. and LS9, Inc. have developed engineered microbes that produce fatty alcohols for detergents.

AFFECTED COUNTRIES/REGIONS: 58% of global oleochemicals production is in Asia, as is most production of coconut and palm kernel nuts. Babassu palm is grown in Brazil. Countries most affected will be the Philippines, Malaysia, Indonesia and India. Vietnam, Mexico, Nigeria, Thailand and Papua New Guinea also have sizable coconut and palm kernel production. In the Philippines, approximately one quarter of the population depends on coconut production, impacting around 25 million people.

MARKET: The global market for natural fatty acids (primarily derived from coconut, palm and palm kernel oil) was valued at $7.2 billion in 2011 and is expected to reach $13 billion by 2017. The market for lauric acid alone was estimated at about $1.4 billion in 2008; the market for myristic acid is estimated at about $600 million. In 2011, the market for palm kernel oil was estimated at $9.3 billion and coconut oil at $5.3 billion. This is just part of a larger $206 billion plant oils market that new SynBio companies are hoping to capture. Detergent alcohols in particular are a $6 billion market worldwide, expected to reach $8 billion in a decade.

COMMERCIALIZATION: Solazyme already has a production facility in the USA and has partnered with a number of key players to begin commercialization of its lauric oils. These partners include chemical giant Mitsui, household products transnational Unilever, grain traders Archer Daniels Midland and Bunge, as well as chemical firm AkzoNobel. Solazyme may have the technical capacity to capture up to 40% of global myristic acid production in the coming years with a new 100,000 MT/annum (metric tonnes per year) plant under construction in Brazil in collaboration with Bunge. Codexis is already selling small quantities of its CodeXol fatty alcohols and is hoping to have a 60,000 MT/annum commercial production plant running by 2015. In 2012, LS9, Inc. produced 135,000 litres of synbiotech-derived fatty alcohols and is now scaling up to supply customers, including Procter & Gamble.

NATURAL OLEOCHEMICALS

Oleochemicals are those chemical products produced from oils, a large part of whose market is for "natural oleochemicals" that refine vegetable oils into detergents, soaps, shampoos and other household goods. An important range of starter compounds for oleochemicals is the natural fatty acids known as "lauric oils." For these, coconut oil and palm kernel oil (different from palm oil, which comes from the pulp of the palm fruit) are the major raw material sources, occasionally supplemented by small amounts of babassu oil, derived from the Brazilian babassu palm.

Coconut oil, produced from crushing the copra (flesh of matured fruit) of harvested coconuts is particularly rich in lauric oils and supplies much of the oleochemical market. Coconut oil consists of about 48% lauric acid, 16% myristic acid and 9% palmitic acid. It is also a good source of capric or caprylic acid. Coconut oil and palm kernel oil are also the major industrial sources for C12-C14 fatty alcohols (C12-C14 refers to the length of the chain of carbon molecules), such as lauryl alcohol and myristyl alcohol; these are used primarily for detergents. The largest users of coconut- and palm kernel-derived detergent alcohols are consumer products companies, including US-based Procter & Gamble, Netherlands-based Unilever and Germany-based Henkel.

COCONUT OIL PRODUCTION IN THE PHILIPPINES AND BEYOND

Known in the Philippines as "The Tree of Life," the coconut tree (Cocos nucifera) is celebrated for its many uses, from food and clothing to building materials. However, it is the copra crushed into oil that is primarily sold internationally as a commodity both for food and more commonly for detergents, soaps, etc. Global production of coconut oil is estimated at 3,735,000 MT for 2013 with over 90% of that grown in Asia and the South Pacific. On average, 1000 coconuts yield 110 kg of oil.

The Philippines is the world's leading producer of coconuts, accounting for 46.2% of global coconut oil production and 59% of the world's coconut exports. There are around 3.5 million coconut farmers and as many as 25 million people are directly or indirectly dependent on the coconut industry, which spans cultivation, harvesting, transport, processing and trading. Coconut farming is distributed across the entire country: of 79 provinces, 68 are coconut-growing areas and coconut is grown on 26% of Philippine farmland (~324 million trees). The coconut farms of the Philippines are relatively small, with an average area of 2.4 hectares (ha). About two-thirds of the country's 1.4 million coconut farms are owner-operated. Coconut cultivation in the Philippines generally does not require chemical inputs, and other crops are often grown together under the tall trees' shade. Despite their contribution to the country's annual GDP, poverty incidence among Filipino coconut farmers is about 62%, due to stagnation of copra prices since 2010 and low wages for workers. Other major coconut-producing countries include Indonesia (26.1% of world coconut oil production), India (12%) Vietnam (4.1%) and Mexico (3.9%).

PALM KERNEL OIL PRODUCTION

About 74% of the world's production of palm oil is used for food; the remaining 26% is used for industrial products. When the fruit of oil palm trees is processed into palm oil, the seed is kept aside and crushed separately into "palm kernel oil" (PKO). Consequently, the palm kernel oil market is closely tied to the palm oil market. PKO is high in lauric oils and is commonly used as an ingredient in processed foods due to its relatively low cost and ability to withstand high cooking temperatures. Currently 86% of the world's supply of palm oil comes from large industrial plantations in Indonesia (7.65 million ha) and Malaysia (4.917 million ha). Those two countries dominate palm kernel oil production. Smaller amounts are grown in Nigeria, Thailand, Colombia and Papua New Guinea.

REPLACING PALM KERNEL OIL WITH SYNBIOTECH SUBSTITUTES!

The past ten years have seen a significant increase in palm oil plantings due to the growth in support for biofuels, through direct and indirect subsidies. This has raised much concern about the accompanying destruction of forests, particularly ape habitats, release of carbon from cleared peatland and the impact on migrant workers and forest communities. According to Friends of the Earth, some estimates show an area the size of Greece being cleared every year for palm oil plantations and investigations by the CSO Grain uncovered land grabs (millions of hectares) for oil palm plantations across Asia, Africa and South America. Because of the environmentally destructive profile of palm oil (including palm kernel oil), some of the corporate investments in producing lauric oils through synthetic biology have been promoted as environmentally beneficial. In 2010, Unilever, the world's largest user of palm oil, announced a multimillion dollar investment in Solazyme, signalling that the move was environmentally motivated: "To Wash Hands of Palm Oil Unilever Embraces Algae: Consumer-Goods Maker Invests in California's Solazyme to Avoid Environmental Concerns," announced the *Wall Street Journal*. While moving away from destructive palm oil is to be welcomed, any supposed environmental gain needs to be weighed against these considerations:

1) Switching from palm kernel oil to synthetic biology-derived fatty acids doesn't directly slow the market for palm oil. Indeed, given the growing interest in palm oil for biofuels and the concentrated nature of the market, the price of palm kernel oil may prove quite elastic. If so, the coconut oil market may suffer more.

2) The environmental benefits of switching from monoculture palm may be offset by the increased use of agricultural sugars as feedstocks for the synthetic organisms producing the oil. Sugar production, like palm production, is associated with land clearance for intensive monocultures, large scale releases of greenhouse gases, significant agrochemical use and poor working conditions for sugar workers. Sugarcane expansion in Brazil has been implicated in pushing the agricultural frontier deeper into the Amazon, begging the question of whether Unilever's investment in Solazyme ultimately implies only a change of scenery: forest destruction in Indonesia to forest destruction in Brazil.

BABASSU OIL PRODUCTION

Babassu oil is extracted from the kernels of the Babassu palm tree, which originates in the Amazon and is grown widely in the Brazilian states of Maranhão and Piauí. The oil's properties are similar to coconut oil's; babassu oil contains 50% lauric acid and 20% myristic acid. Babassu palm is an aggressive weedy species able to flourish in different ecosystems and can form forest-like expanses of millions of hectares that look like plantations but are in fact naturally seeded.

Removing Babassu kernels is labour-intensive, and is traditionally carried out by women known as "Babassu crackers" who sell the kernels to traders who, in turn, sell to industrial oleochemical processors. According to Biofuels Digest, more than 400,000 women and their families process the palm for oil, soaps, flour and animal feed. Babassu oil is generally not traded internationally; most of the oil produced is reserved for Brazilian cosmetics.

CURRENT STATE OF SYNTHETIC BIOLOGY ALTERNATIVES TO FATTY ACIDS AND ALCOHOLS SOLAZYME: MAKING FATTY ACIDS IN ALGAE

Solazyme, Inc. of California, USA is a publicly-traded synthetic biology company with a business plan to engineer algae in order to change the chemical profile of algal oil. Unlike most algae companies, Solazyme works with heterotrophic algae: strains that feed on sugar instead of sunlight and so can be grown in closed vats in an industrial facility rather than shallow

Top 10 Coconut Oil Producing Countries / 2013 Estimate[17]

Country	Production 2013 (1000 MT)	Market Share (% of world production)
1. Philippines	1,725	46.2
2. Indonesia	974	26.1
3. India	447	12
4. Viet Nam	153	4.1
5. Mexico	145	3.9
6. Papua New Guinea	63	1.7
7. Thailand	46	1.2
8. Sri Lanka	43	1.1
9. Malaysia	35	0.9
10. Mozambique	30	0.8
Total top 10	***3,661***	***98%***

Estimated world coconut oil production for 2013: 3,735,000 MT

ponds. While Solazyme was initially founded as a biofuels business, like many synthetic biology companies, it has shifted its business plan to produce natural compounds, flavours and food ingredients. Solazyme has engineered its algae to produce a range of "genetically tailored oils," which each express high levels of a particular fatty acid. The company claims it has developed algal strains that express up to 80% of their oil as lauric oils (cf. palm kernel oil's 55% lauric oils and coconut oil's 68%). Solazyme claims that an oleochemical facility utilizing its tailored oil rather than standard palm kernel oil could increase output of the desired fatty acid components such as capric, lauric and myristic acid by more than 30%.

Top 10 Palm Kernel Oil Producing Countries / 2013 estimate[26]

Country	Production 2013 (1,000 MT)	Market Share (% of world production)
1. Indonesia	3,588	52.8
2. Malaysia	2,180	32.1
3. Nigeria	305	4.4
4. Thailand	190	2.8
5. Columbia	100	1.4
6. Papua New Guinea	60	0.9
7. Ecuador	51	0.7
8. Brazil	43	0.6
9. Côte D'Ivoire	39	0.6
10. Cameroon	32	0.5
Total top 10	***6,588***	***96.8%***

Estimated world palm kernel oil production in 2013: 6,796,000 MT

In particular, Solazyme trumpets its ability to compete against natural coconut oil as a better source of myristic acid. According to Solazyme, coconut oil can sometimes reach concentrations of up to 15% myristic acid. By contrast, Solazyme's engineered algal oil currently boasts 60% concentration of myristic acid, almost four times more than any widely available oil today. As market analyst Kevin Quon points out:

> "This results in more than a 150% increase over that which is found in coconut oil. Through rough calculations, it would appear that in order to get 1 MT of myristic acid, it would either take 2.5 MT of tailored algal oil yielding 40% or it would take 6.67 MT of coconut oil yielding 15%. If we were looking just for myristic acid, it would therefore take 63% less oil in order to get it from Solazyme's tailored algal oil."34

Solazyme says their lauric oils will become commercially available toward the end of 2013.

Sugar, like palm, is associated with land clearance for intensive monocultures, large scale releases of greenhouse gases, significant agrochemical use and poor working conditions.

How Solazyme's algal myristic acid will fare against coconut-derived myristic acid in the marketplace depends in part on coconut oil prices and sugarcane prices (sugar is the feedstock for the company's engineered algae). Solazyme is keen to point out that while most coconut is sourced from the Philippines and takes several years to grow, sugarcane can be grown quickly in many locations, including in coconut- producing countries such as the Philippines. In time, Solazyme hopes to feed cheaper cellulosic sugars to their algae (e.g., grasses or wood pulp): "...oil supply can be unlocked from a regional land restriction. Instead, the range is increased to include anywhere in which more-readily abundant sugarcane is grown. Once the ideal infrastructure is developed, it can even be produced at any location where cellulosic biomass is found."

Solazyme has told investors that it would be able to manufacture oils at a cost below $1000 per MT if produced in a built-for-purpose commercial plant, although they currently plan to sell their myristic acid for around $3000/MT. Today, myristic acid sells for more than $4200/MT. Solazyme is moving ahead with building at least two large commercial plants: a facility in Illinois, USA producing approximately 500,000 gallons (1.89 million L) of oil/annum and a facility in Brazil able to ferment over 28 million gallons/annum (105 million L). At 60% concentration, the Brazilian facility alone would theoretically be able to meet about 40% of global myristic acid market.

Solazyme has signed a number of joint ventures and agreements with some of the world's largest sugar, chemical and oleochemical players, including Bunge, Archer Daniels Midland, Dow, Akzonobel and Mitsui. The $20 million Mitsui deal is especially relevant for coconut and palm kernel oil markets since it focuses specifically on the further development of high myristic algal oil. Mitsui has been producing oleochemicals for 20 years through its subsidiary Palm Oleo and is a significant investor in Kuala Lumpur Kepong Berhad (KLK), which owns palm oil and rubber plantations and is the world's largest oleochemical company. On signing the multi-year deal, Mitsui stated that it "looks forward to strengthening its position in the oleochemicals industry through the successful development and commercialization of these novel products." Solazyme also has an agreement with Unilever, one of the world's largest end-users of oleochemical ingredients for production of consumer soaps and detergents. In this way, Solazyme appears to have secured partners all along the supply chain–from initial sugar to final consumer product.

CODEXIS AND LS9: MAKING FATTY ALCOHOLS IN MICROBES

Codexis is a synthetic biology company using computer-based techniques to artificially "evolve" and re-engineer enzymes and microorganisms. LS9, founded by leading SynBio researchers Jay Keasling and George Church, is focused on engineering microbes–primarily E. coli–to produce industrial compounds. Both are based in California and both were initially focused on biofuels but are now moving into other markets. Both companies have developed the technology to produce fatty alcohols. According to Codexis, so-called "detergent alcohols" for use in household products represent a $6 billion market worldwide, expected to reach $8 billion in a decade.

While there is a range of different fatty alcohols, the popular C12-14 alcohols, known as lauric alcohols, are usually derived from coconut oil and palm kernel oil. Codexis has developed a microorganism that produces a new lauric alcohol dubbed CodeXol and in collaboration with Chemtex, a subsidiary of Italian chemical company Gruppo M&G, is scaling up production of CodeXol; they aim to reach full- scale commercialisation by 2015.In June 2013, Codexis and Gruppo M&G announced that they had successfully scaled up

a process that would transform cellulosic biomass into lauric alcohols. In theory, this would allow Codexis to produce a competitor to coconut- and palm kernel oil-derived detergents using so- called agricultural "waste" and forest "residues" as feedstock.

LS9 has agreements with Procter & Gamble and a facility in Florida, USA that produces 135,000 liters of fatty alcohols at a time and has reportedly been producing batches for commercial partners. LS9 plans three 750,000-liter fermenters in Brazil, which could produce 10,000-25,000 MT/year of fatty alcohols, while a large-scale commercial facility is expected (in 2017-2018) to have a capacity of 200,000 MT/year.

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For a list of sources cited in this case study, email *info@etcgroup.org*.

Ginseng

A *Draft* Case Study

Product: the hairy root of Ginseng (*Panax ginseng* C.A. Meyer) has been used for over 4500 years in Eastern medicine to counter stress, disease and exhaustion. It is also eaten as a food.

Status: There are active research projects in Belgium and China successfully using synthetic biology to produce **ginsenosides** (the active compound in Ginseng) in engineered yeast and in other plants. Additionally, American-Swiss synthetic biology company Evolva Inc. has confirmed that it is targeting Ginseng as a commercial product.

Affected Countries: Four countries–South Korea, China, Canada and the US–are the biggest producers of Ginseng, accounting for over 99% of the global harvest. Culturally, Ginseng is most significant for South Korea, which is the world's largest consumer of ginseng as well as its second largest producer. In South Korea, ginseng is distributed and used widely and is commonly consumed as a food. China is the world's largest producer with annual production of 44,749 tonnes, It is followed by South Korea (27,480 tonnes), Canada (6,486 tonnes), and the US (1,054 tonnes). It takes 4-6 years to grow Ginseng for harvest.

Market: Today the world Ginseng market–including ginseng root and processed products–is estimated to be worth $2,084 million. In particular, the size of the Korean market is $1,140 million. Korea exports $38 million (2009 figures).

Commercialization: Ginseng produced by synthetic organisms is still at proof of concept stage. Currently there is no announced commercialization but there may be a Chinese product.

Background: ***Panax Ginseng*** is an Asian root crop widely used in health foods for its wide range of claimed medicinal properties and is of particular cultural importance to Korea and China. It is a slow-growing herbaceous plant whose roots are said to resemble the shape of a person (hence "ginseng" means "person root"). Ginseng is now receiving attention from Synthetic Biologists interested in engineering microbes and crops to replace the Panax Ginseng plant. The focus of interest are Ginsenosides, at least 8 active compounds that accumulate in the ginseng root. The compounds of interest are known as Rb1, Rb2, Rc, Rd, Re, Rf, Rg1 and Ro and they are from a class of compounds called *Triterpenoid saponins* which are isoprenoid compounds. A number of research groups and private companies have already built and commercialized synthetic organisms able to produce other isoprenoids in vats and in the quest for commercially valuable isoprenoids ginsenosides are now becoming an attractive industrial target.

Jars of ginseng. *photo: SnippyHolloW*

80,080 tonnes of botanical Ginseng are produced annually worldwide with production almost entirely in four countries (China, South Korea, Canada and USA). Growing a ginseng root for harvest takes 4-6 years and requires that a new root is planted on land that did not have ginseng the previous year. As such, farming ginseng is tricky and requires patience. In an effort to circumvent growing challenges and assure availability of ginsenosides for foods and medicines there has already been considerable research and development of laboratory cell cultures for ginseng. A few tonnes of tissue-cultured Ginseng are currently being sold in the Korean market but the technique is low-yielding and the market remains overwhelmingly botanically-derived. The arrival of synthetic biology techniques marks a new rival for ginseng farmers.

Current R&D: At least three research teams and one commercial company have set their sights on producing synthetically-derived ginsenosides by fermentation.

In 2012 a team of bioengineers from Jilin University in China led by YL Liang published a paper showing that they had successfully engineered bakers' yeast to produce the compound *dammarenediol* which is the key precursor for ginsenosides. The researchers report that "engineered microbial systems producing ginsenosides or a ginsenoside precursor, which can be transformed to ginsenosides, should facilitate practical production of ginsenosides by providing an inexpensive and environmentally benign alternative to extraction from ginseng roots". In an online marketing presentation, the research team boasts that unlike the 6 years required to grow natural ginseng "Our Ginsenoside based product "Xinseng" will take only a few days to produce through our patented synthetic biology processes" and that Xinseng will be available as powder, capsules or liquid form as "a substitute for cultivated ginseng". It is not clear if Xinseng is already a commercialized product.


Jennifer Dunne

Another Chinese team published a paper in Nature in January 2014 showing that they had also engineered yeast to produce three key ginseng precursor compounds (Protopanaxadiol, protopanaxatriol and oleanolic acid). They boasted that "The yeast strains engineered in this work can serve as the basis for creating an alternative way for producing ginsenosides in place of extractions from plant sources."

Meanwhile a Belgian team at the University of Ghent is developing a combinatorial synthetic biology platform to engineer yeast as well as clover plants to produce a variety of key compounds including ginsenosides. According to the group's homepage, they hope to serve the needs and demands of the pharmaceutical, agrochemical and nutreaceutical industries: "The ultimate aim is to create a "rainforest"-like metabolic diversity within a few performing organisms in the laboratory, which will allow launching a new era of bioprospecting of the metabolic richness of the plant kingdom."

At the same time, leading Synthetic Biology company Evolva SA of Switzerland has an active interest in engineering yeast to produce Ginseng compounds. Evolva has partnered with leading food, fragrance, cosmetic and chemical companies such as International Fragrance and Flavours, Cargill and L'Oreal to bring a range of food and flavouring ingredients such as vanilla, stevia and resveratrol to market. In its presentations to investors, Evolva lays out a full list of natural products that it aspires to replace, including Ginseng, as part of what it calls the Evolva "metro" of target compounds and has confirmed to ETC group that it is actively working on ginsenosides. Much of Evolva's partnership with food, cosmetic and ingredients companies is to develop undisclosed compounds for their private clients so it is not known if Evolva's work on ginsenosides is part of an agreement with one of these companies.

Another Synthetic Biology company that currently produces isoprenoids and may be well placed to develop SynBio-derived ginsenosides is Amyris Inc of California USA. Amyris already commercially sell a SynBio derived squalane - a substance that can be converted biochemically into ginsenosides. Like Evolva, Amyris is also developing undisclosed compounds for private companies to commercialize.

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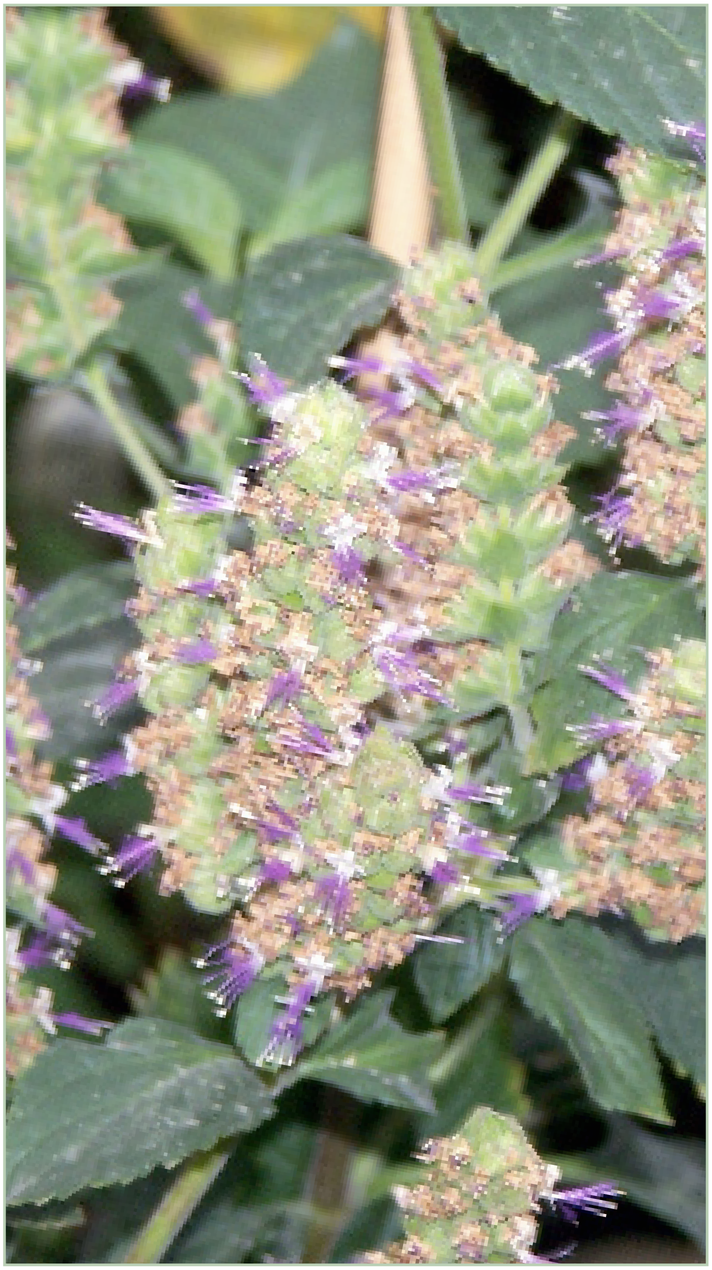
For a list of sources cited in this case study, email *info@etcgroup.org*.

Patchouli

A SynBio Case Study



Product: Part of the mint family, the patchouli plant (*Pogostemon cablin*) is native to tropical Asia, where it is mainly grown Indonesia is the main supplier with two thirds of global production (mainly on the island of Java), followed by China and Malaysia. Patchouli is believed to have originated in the Philippines.
To extract patchouli oil from the plant's leaves to a commercial standard requires the use of a solvent and a distillation process. Known for its distinct fragrance and frequently used in perfume and incense, patchouli oil can be found in laundry detergents, air fresheners, baby wipes, and more.

Status: Patchoulol, the key component patchouli oil, has been produced through synthetically altered microorganisms by California-based biotech company Amyris in partnership with Firminich, the Swiss purveyor of perfumes and flavours. The companies say they have developed a novel bioprocess for producing large, quality volumes of patchouli oil from yeast and are currently doing so in Amyris's facility in Brotas, Brazil.

Affected country/region: the smallholders and small farmers of Malaysia, China,Indonesia and Singapore will inevitably be affected by Amyris's new product. With this new product, Amyris aims to replace the lengthy cultivation and extraction process with a single manufacturing process that produces patchouli oil in about two weeks.

Market: long-term contracts for dried leaves can fetch \$300-\$350 per metric ton, but purified patchouli oil can fetch \$50 per kilogram. Consumption of patchouli oil in the world is about 1,000 tonnes per annum.

Commercialization: The product Clearwood, a new woody ingredient produced from the fermentation of sugar cane, sourced from Brazil, is being marketed by Firmenich as a total or partial replacement for patchouli oil. The product may be in use in consumer goods like perfumes or other scented products.

Current R&D: In April 2014, the US company Amyris restarted its industrial fermentation site in Brotas, Brazil with the plan of adding patchoulol to its existing farnasene production process. For Amyris and Firminich, synthetically-derived patchouli will help mitigate and help to solve supply chain problems.

Rubber

A SynBio Case Study

Tapping a rubber tree. *photo: Dhruvaraj S*

Product: Rubber is the tropical plant-derived product receiving the most attention from synthetic biology companies. Several labs are working to scale up production of biosynthetic isoprene, as well as butadiene and isobutene, all components in the manufacture of synthetic rubber. The goal is to manufacture commercial-scale quantities that will compete with both natural and synthetic rubber.

Status: Several commercial teams are using synthetic biology to manufacture isoprene in microbial cell "factories" via fermentation; DuPont and Goodyear have already produced a prototype tire using biosynthetic isoprene. France-based Global Bioenergies has produced both bio-butadiene and bio-isobutene using engineered metabolic pathways in bacteria. In May 2012, Bridgestone announced joint development of synthetic rubber made from isoprone with the the Japanese company Ajinimoto.

> *"The process... offers the possibility for obtaining the quantities of low-cost isoprene needed to produce... [an] alternative to Hevea natural rubber."*
>
> – Frank J. Feher,
>
> *Rubber & Plastic News, Nov 1, 2010*

Affected Country/Region: 20 million smallholder families rely on rubber trees (*Hevea brasiliensis*) for their livelihood. The rubber industry in Southeast Asia is characterised by the preponderance of small farmers who own and cultivate some 67 percent of the total planted area in Malaysia, 78 percent in Indonesia, 95 percent in Thailand and 65 percent in Sri Lanka. Most of the smallholdings are less than 10 acres apiece and are widely scattered.
Cambodia, China, India, Indonesia, Malaysia, Papua New Guinea, Philippines, Singapore, Sri Lanka, Thailand and Vietnam accounted for about 93% of the global production of natural rubber during 2013. The global market for natural rubber was approximately $35 billion in 2010. In 2012, the total area dedicated to natural rubber production in the world was 9.56 million hectares.

Market: Current demand for isoprene: 850,000 tons per year, with a market value of $2 billion. (The demand is likely to grow faster in 2014; Demand for natural and synthetic rubber will hit 27.7 million tonnes this year.

Commercialization: Products are either on the market or will be imminently as of 2014.

About Rubber

Rubber is the tropical, plant-derived product receiving the most attention by synthetic biology companies. A major focus is *isoprene*–the molecule that is a crucial building block for making synthetic rubber. The gene encoding *isoprene* has been identified only in plants such as rubber trees. In 2010, DuPont subsidiary Genencor announced that it had used synthetic biology to produce "BioIsoprene." Its goal is to manufacture BioIsoprene cheaply and in commercial-scale quantities via fermentation to compete with both natural and synthetic rubber.

Top 5 Natural Rubber Producers (end of 2012)

Country	Natural Rubber Production (millions of MT)
Thailand	3.6
Indonesia	3
Malaysia	0.95
India	0.9
Vietnam	0.9

Source: (Natural Rubber Industry Vietnam).

Asia is by far the largest producer of natural rubber. In 2013, global natural rubber production was 12 million metric tons (MT). Five Asian countries accounted for 83% of all natural rubber produced worldwide. According to the International Rubber Study Group 80% of all natural rubber is produced by small holders who farm an average 1 to 2 hectares. Globally, an estimated 20 million small holder families rely on natural rubber for their livelihoods.

Current R&D

Synthetic rubber is typically made from chemical synthesis of petroleum-derived isoprene. Companies are now competing to develop the most efficient metabolic pathway for producing a cheaper version of isoprene via biosynthesis in engineered microbes. Global Bioenergies is developing bio-based isobutene and is collaborating with Poland-based rubber manufacturer Synthos to commercialize bacterial biosynthesis of bio-butadiene. The goal is to reduce the tire industry's dependence on petroleum-derived synthetic rubber, and, perhaps, to capture some portion of the market for natural rubber.

photo: Yun Huang Yong

The tire industry is the driving force behind changes in demand for natural rubber. Although natural rubber is more easily replaced by synthetics in non-tire applications, natural rubber is still a vital–and thus far irreplaceable–component in tires. More than 60 percent of all natural rubber is used for tires, and the content of tires is typically 50% natural rubber. BioIsoprene has already been used to manufacture prototype tires: According to a report in Industrial Biotechnology, "Current state-of-the-art technology has resulted in production, recovery, polymerization, and manufacture of tires with the isoprene component produced via fermentation. Continued improvements in both the cell factory and the production process are being actively pursued."

Intellectual Property related to Isoprene Rubber Pathway Engineering:

EP1472349B1: Methods for Multiple Parameter Screening and Evolution of Cells to Produce Small Molecules with Multiple Functionalities. Evolva AG. 29 Oct 2008.

EP1364005B1: A Method for Evolving a Cell Having Desired Phenotype and Evolved Cells. Evolva AG. 17 Sept 2008.

WO2011146833A1: Method of Producing Isoprenoid Compounds in Yeast. Evolva. 24 Nov 2011.

It is too early to predict if bio-isoprene has the potential to capture a portion of the market for natural rubber. But scientists who are working on BioIsoprene indicate that the product "has the potential to provide a large-volume alternative to Hevea natural rubber and petroleum-derived isoprene."

References

For a list of sources cited in this case study, email *info@etcgroup.org*.

Saffron

A SynBio Case Study

The crocus flower. *photo: Linda Hartley*

Product: Saffron, the world's most expensive spice, is derived from the crocus flower, *Crocus sativus*. Saffron is a food flavouring and coloring agent.

Status: Evolva, a Swiss synthetic biology company, has completed an R&D process and is moving toward commercialization. The company has identified and built the metabolic pathways that result in three of saffron's key chemical compounds related to colour and flavour. The pathways are inserted into microbes to produce the compounds through fermentation, bypassing the need for crocus flowers.

Affected Country/Region: Iran accounts for over 90% of world saffron production. Spain, India, Morocco, Greece, Turkey, Kashmir and Afghanistan are minor producers.

Market: World production of saffron is estimated at 300 tonnes *per annum*. Based on current average market prices of USD $1,500/kg, the market is worth some $450 million.

Commercialization: Evolva expects products to be available in 2015 or 2016.

The world's most expensive spice, saffron is derived from the dried stigma of the crocus flower, *Crocus sativus*. Saffron is prized as a flavouring and coloring agent for food. The chemical constituents of saffron, including crocin and crocetin (colors), picrocrocin (bitter principle) and safranal (flavor), also have

The company has built metabolic pathways that result in three of saffron's key chemical compounds related to colour and flavour.

health benefits.

90-95% of the crocus flowers used to produce saffron are grown in Iran. It takes 250,000 crocus flowers and 40 hours of labor to manually extract enough stigmas to yield 1 kilogram (kg) of saffron. After pistachio, saffron is Iran's most important non-petroleum export product. During harvest, each hectare devoted to saffron provides jobs for up to 270 people per day. Good quality saffron sells from $2,000 to $10,000/kg or more. Annual worldwide sales of saffron are an estimated $660 million. In 2009/2010, Iran's northeastern Khorasan Razavi province exported 57 tons of saffron worth $156.5 million to 41 countries.

Harvesting crocus flowers.

Current R&D

In 2010, Swiss-based synthetic biology company Evolva began working on a biosynthetic route to express saffron-derived genes in engineered microbes. The goal is to build a novel metabolic pathway that instructs cells to produce key saffron compounds, which is then inserted into a microbial host for large-scale production in fermentation tanks (bioreactors). According to the company:

> Producing the key saffron components by fermentation has three main benefits. Firstly, it will allow saffron to be available at a much lower price than currently, which will both expand existing markets and open new ones. Secondly it will eliminate the many complexities involved in the current supply chain. Finally by making each of the key components separately it will enable the production of customized forms that are for example particularly rich in aroma, taste or colour and that can be adapted to specific food formulations and regional preferences.

Evolva conducts R&D on saffron at its location in Chennai. The company claims that it is now in the process of "pathway optimization" and predicts that a commercial saffron product will be available in 2015 or 2016.

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For a list of sources cited in this case study, email *info@etcgroup.org*.

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Squalane

A SynBio Case Study

Most squalane is currently produced from olives. *photo: Marco Bernardini*

Product: Squalene is a high-end, oil-free moisturizing ingredient used in many cosmetics that, until recently, was extracted primarily from the liver of deep sea sharks.

Status: California-based synthetic biology company, Amyris, Inc., has engineered the metabolic pathway of yeast to produce a molecule called farnesene–an essential building block for a wide range of chemical products–including squalene.

Affected Country/Region: Deep-sea trawlers are losing out to Spain and other Mediterranean area exporters who, in turn, may lose out to Brazil's sugarcane industry. Instead of sourcing squalene from shark liver oil, the moisturizer can be extracted from botanical sources, including rice bran, wheat germ, amaranth seeds and olives. Refined olive oil is now the primary botanical source for squalene but synthetic biology may allow the market to shift to sugarcane in Brazil.

If synthetically-derived squalane makes it to market, Spain and other Mediterranean exporters may lose out to Brazil's sugarcane industry

Market: The squalane market has shrunk to just one third of its size by volume in the last decade. Global squalane production was 2,500 metric tonnes (MT) in 2013. Of that, 1,050 MT is produced frome olive oil, 1,000 MT from shark liver, and 450 MT from Amyris. At current prices, the market represents $93 million in sales.

Commercialization: Amyris, Inc. is selling commercial quantities of squalene to cosmetic ingredient buyer Soliance (France). Engineered microbes in Amyris' Brazil-based fermentation facility produce farnesene and byproducts such as squalene from up to two million tons of crushed sugarcane per annum. Amyris has selected Dowell C&I Co., Ltd., a supplier of ingredients for the personal care industry, as its exclusive distributor of Neossance™ Squalane in the Republic of Korea. The company is planning to double its sugar-based squalene sales in 2014.

About Squalane

Squalene is a high-end, oil-free moisturizing ingredient used in a wide variety of cosmetics that, until recently, was extracted primarily from the liver of deep-sea sharks. The livers of an estimated 3,000 sharks are required to produce just 1 ton of squalene.[1] Up to 6 million deep-sea sharks a year were thus killed to meet the global demand of between 1,000-2,000 tons per annum.[2] Squalene is also used in the manufacture of vaccines.

As a result of civil society campaigns deep-sea shark harvesting is now prohibited in many parts of the world and, remove shark squalene from their cosmetic brands in favor of renewable plant-based sources.[3] Recent advances in the purification of squalene have allowed perennial botanical sources like olives to become a viable commercial alternative to sharks.[4]

Refined olive oil is now the primary botanical source of squalane.[5] In 2008, L'Oreal and Unilever announced that they would remove shark squalene from their cosmetic brands in favor of renewable plant-based sources.

Olive oil, received from the first compression, holds about 400-450 mg per 100g of squalene, while refined oil contains about 25% less. In some cases, premium quality olive oil contains concentrations of up to 700 mg per 100g.

Current R&D:

Amyris has used synthetic biology to engineer the metabolic pathway of yeast to produce a molecule called farnesene, an essential building block for a wide range of chemical products which can then be processed into large amounts of high-quality squalane. In February 2010 Amyris announced that it was selling its 100% bio-based Neossance™ Squalane–the company's first commercial product–to Soliance, a provider of ingredients to the French cosmetic industry.[6]

According to the company's plan, the Brotas facility in Brazil is capable of producing their synthetic farnesene–they call it Biofene–from up to two million tons of crushed sugarcane annually.[7] The Brotas facility is also producing patchouli oil. Amyris is reportedly scaling-up production of microbial-derived farnesene at production facilities in Brazil, US and Europe.[8] The company has not disclosed production costs or capacity related to squalene.

Intellectual Property related to Biosynthesis of Squalane:

[US20120040396A1: Methods for Purifying Bio-Organic Compounds. Assignee: Amyris, Inc. Published: 16 Feb 2012.

WO2012024186A1: Method for Purifying Bio-Organic Compounds from Fermentation Broth. Assignee: Amyris, Inc. Published: 23 Feb 2012

US20100267971A1: Stabilization And Hydrogenation Methods For Microbial-Derived Olefins. Assignee: Amyris, Inc. Published: 21 Oct 2010.

WO2010115097A3: Stabilization And Hydrogenation Methods For Microbial-Derived Olefins. Assignee: Amyris, Inc. Published: 29 Sept 2011.

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7 Anonymous, 2010. "Amyris: Farnesene and the pursuit of value, valuations, validation and vroom," Biofuels Digest, June 25, 2010.
8 Andrew McDougall, Amyris receives multi-million dollar approval for first industrial-scale production facility in Brazil, CosmeticDesign.com, 28 November 2011. http://www.cosmeticsdesign.com

The facility in Brazil is capable of producing their synthetic farnesene from up to two million tons of crushed sugarcane annually.

Star Anise

A SynBio Case Study

Product: Shikimic acid is the key raw material for the manufacture of oseltamivir (Tamiflu), an anti-viral drug. Shikimic acid is traditionally sourced from star anise, the pod of the Chinese medicinal plant, Illicium anisatum.

Star anise seed pods. *photo: Arria Belli*

Status: After the outbreak of bird flu in 2005 demand for Tamiflu soared because countries began stockpiling the drug. Because of a shortfall in supplies of botanically-derived star anise, synthetic biologists began engineering the metabolic pathway of bacteria to produce shikimic acid via fermentation.

Affected Country/Region: China produces about 80% to 90% of the world's star anise. Chinese farmers are heavily affected by fluctuating commodity prices and new synthetic technologies.

Market: In 2005, the price of Chinese shikimic acid derived from star anise soared to more than $400/kilogram, from $40/kg. Worldwide sales of the anti-viral drug fluctuate: in 2009 Tamiflu sales were $2.9 billion; in 2011 sales reached only $406 million.

Commercialization: Most of the shikimic acid used by Roche, a Swiss pharmaceutical company, to manufacture Tamiflu is now sourced from microbial fermentation. Roche has contracts with Sanofi Aventis (France) and others to provide the shikimic acid produced in "cell factories."'

"For our Tamiflu production we mostly rely on the microbial fermentation process."

Plant-Derived Pharmaceutical Ingredients, Rio+20 and Technology Assessment

This case study illustrates how a key pharmaceutical ingredient, shikimic acid–traditionally derived from star anise cultivated by Chinese farmers–can be rapidly replaced by a new technological production process. Using synthetic biology, shikimic acid is now being produced commercially in drug industry fermentation tanks. The transition took less than a decade. Shikimic acid is just one example of a raw material that may be affected; it is conservatively estimated that at least 50% of today's commercial pharmaceutical compounds are derived from plants, animals and microorganisms. A decision at Rio+20 to establish UN technology assessment could alert exporting countries to risks, opportunities and alternatives in advance of market disruptions.

The production of a major anti-viral drug, Tamiflu, depends on shikimic acid, which is traditionally sourced primarily from star anise, the star-shaped pod of the traditional Chinese medicinal plant, Illicium anisatum. Roughly 80-90 percent of the world's star anise is grown in southwestern China, primarily in Guangxi and Yunnan provinces. An estimated 66 percent of China's star anise harvest is used to make Tamiflu. (Star anise is also valued as a spice and for medicinal uses.) In Guangxi province alone, some 350,000 hectares of farmland are devoted to the star anise tree with an annual output of 80,000 tonnes. After planting it takes around six years for star anise trees to bear fruit. The process of extracting and purifying shikimic acid from star anise seeds is expensive. It takes about 30 kg of star anise to yield 1 kg of shikimic acid, enough to treat one person. With the heightened threat of global pandemics (bird flu in 2005 and swine flu in 2009) demand for Tamiflu soared and drug company Roche (maker of Tamiflu) couldn't meet demand due to a shortage of star anise. Because of the shortfall in botanically sourced shikimic acid, synthetic biologists and chemists increased efforts to develop alternative production routes in e. coli.

Current R&D

Michigan State University professor, John Frost, founded a small start-up company, Draths Corp., in 2005 to produce building blocks for the chemical, pharmaceutical, and food industries–including shikimic acid. Frost and his co-inventor, Karen Draths, patented a technology for making shikimic acid in engineered e. coli that was subsequently licensed to Roche. Today the co-inventors hold a family of 14 patents and patent applications that cover methods and materials for the production of shikimic acid (see below). In November 2011, Draths Corp. and its intellectual property were acquired by synthetic biology company Amyris, Inc.

By the end of 2005 Roche was reportedly producing about one-third of its shikimic acid supply from the microbial fermentation process. According to Roche, "a specific strain of E. coli which, when overfed glucose, produces SA [shikimic acid]. During the process, the E. coli are fed, fermented, and broken down to extract the SA. Enormous vessels (each the size of 2 city buses) are required to accommodate the volume of E. coli mixture needed."

Roche has continued to increase its fermentation capacity, suggesting that the microbial production of shikimic acid for Tamiflu production is competitive in price with shikimic acid derived from star anise. In March 2012 Roche told ETC Group, "For our Tamiflu production we mostly rely on the microbial fermentation process." The company would not specify the quantity or percentage of shikimic acid derived from microbial production.

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For a list of sources cited in this case study, email *info@etcgroup.org*.

Intellectual Property related to Biosynthesis of Shikimic Acid:

Frost and his co-inventor hold a family of 14 patents and patent applications. These include the first two listed below, for example.

US8080397: Biocatalystic synthesis of quinic acid and conversion to hydroquinone by recombinant microbes. Assignee: Board of Trustees Michigan State University. 20 Dec 2011

US7790431. Methods and materials for the production of shikimic acid. Assignee: Board of Trustees Michigan State University. Published: 7 Sept 2010

US20120052547A1: Methods for control of flux in metabolic pathways through protease manipulation, No Assignee. Published: 1 March 2012.

US20110008867A1: Compositions and methods for the production of a compound. Assignee: GreenLight Biosciences. Published: 13 Jan 2011.

Vanilla

A SynBio Case Study

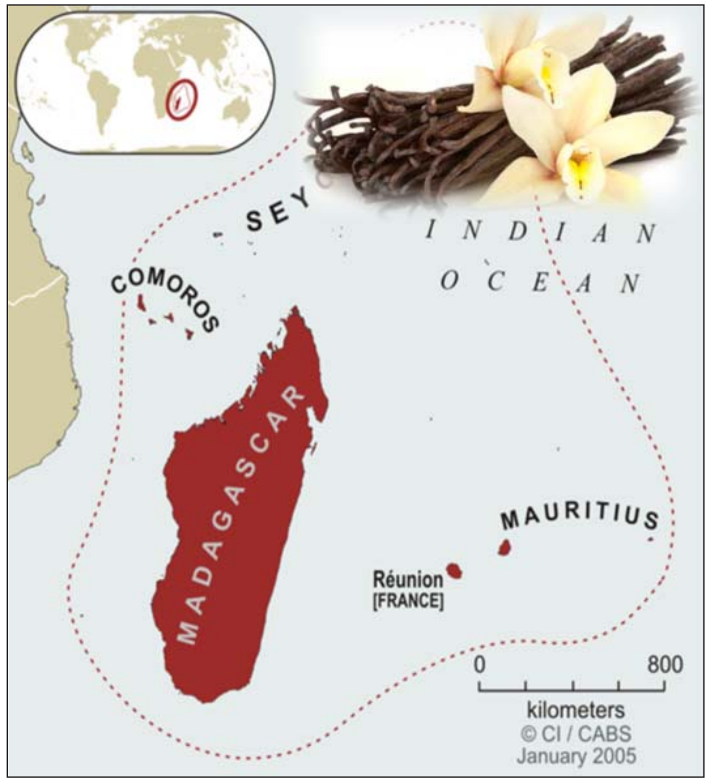
PRODUCT: Natural vanilla flavor/fragrance is sourced from the cured seed pod of the vanilla orchid.

STATUS: Switzerland-based synthetic biology company, Evolva, is partnering with industry giant, International Flavors & Fragrances (USA), to engineer metabolic pathways in microbes to produce key flavor compounds found in vanilla.

AFFECTED COUNTRY/REGION: An estimated 200,000 people are involved in the production of cured vanilla beans per annum. Madagascar, Comoros and Réunion historically account for around three quarters of the world's vanilla bean production. Other producers include: Indonesia, China, Mexico, Uganda, Democratic Republic of Congo, Tanzania, French Polynesia, Malawi, Tonga, Turkey and India.
MARKET: The global vanilla market, both natural and chemically-derived (vanillin), is valued at about $650 million. The value of worldwide trade in vanilla beans is forecast at $150 million in 2013. At the consumer end natural vanilla sells for thousands of dollars per kilogram, synthetic vanillin sells for only tens of dollars.

COMMERCIALIZATION: Evolva and IFF are now scaling up and are "on target" to commercialize a bio-synthesized vanillin flavor in 2014.[1]

Despite high-profile corporate pledges to source raw materials ethically and sustainably, the world's largest brokers of flavor and fragrance ingredients (e.g., Givaudan, Firmenich & IFF) are partnering with synthetic biology companies to develop a new manufacturing platform–"microbial cell factories"–for the biosynthesis of high-value flavor/fragrance molecules, a move that could dramatically reduce botanical imports and banish hundreds of thousands of small-scale farmers, especially in the tropics, from commodity supply chains.



If government regulators permit companies to market new, biosynthesized products as "natural"–consumers may never know if their flavor/fragrances are sourced from small farmers in the tropics or giant fermentation tanks in Northern factories.

"There is potential for biosynthetic routes to completely replace any natural sources."
Kalib Kersh, industry analyst, cited in *Chemical & Engineering News*, 16 July 2012[2]

The synthetic biology platform offers the potential to secure uninterrupted supplies of high-value, flavor/fragrance/ pharmaceutical compounds in industrial- scale fermentation tanks instead of sourcing plant materials from millions of South-based farmers. So-called microbial cell factories are less constrained by geography, extreme weather, crop failures, price volatility–or the farm families whose livelihoods depend on cultivation of high-value botanical exports.

Farming communities in the global South could be affected by biosynthesis-based production of high-value flavors and fragrances. For example: One of the world's largest corporate brokers of flavor & fragrance ingredients, Swiss-based Firmenich, buys over 1,000 natural products every year that come from 170 botanical families in over 50 countries.[3] Givaudan (Switzerland), the world's largest flavor/fragrance company, annually sources more than 10,000 ingredients from around the world.[4] Germany-based Symrise, the fourth-largest supplier of flavor/fragrances, purchased 202,000 tons of raw materials for processing in 2012 from over 100 countries.

"In 2012, the global market for flavors & fragrances (F&F) was $23 billion. The top 4 companies control 56% of the global F&F market."[5]

Natural vanilla–extracted from the cured seed pod of the vanilla orchid (*Vanilla planifolia*)–is a complex flavor made up of more than 150 flavor compounds. "Vanillin" is the most important one. Due to the high cost of vanilla beans, flavor/fragrance companies have long used chemistry to develop a cheaper, chemically synthesized vanillin. Although chemically-synthesized vanillin now accounts for 97% of all vanilla flavor used commercially,[6] the artificial product has not come close to duplicating the complex flavor profile of natural vanilla–which is still in high demand.

Natural vanilla extract from the cured beans of the vanilla orchid is expensive, ultimately selling to the consumer for thousands of dollars per kilogram. By contrast, synthetic vanillin, made from lignin-containing wood pulp waste or from phenol, typically costs $10-20 per kg. The global market for chemically-synthesized vanillin is about 15- 16,000 tons per year, while vanilla derived from vanilla beans represents just 50 tons a year.[7] Synthetic biologists are now using a complex genetic engineering process to modify the metabolic pathway of yeast to produce biosynthesized vanillin in industrial fermentation tanks.[8] The artificially constructed gene sequences involve not just yeast genes, but bacteria, mold, plant and human genes.

Livelihoods at Stake

An estimated 200,000 people are involved in the annual production of cured vanilla beans worldwide.[9] Industry analysts predict that the market for vanilla beans exports worldwide will reach an estimated $150 million in 2013–with African producers accounting for approximately 64% of the total export market.[10]

Production of natural vanilla from vanilla beans is extremely labour intensive: 1 kg of vanilla requires approximately 500 kg of vanilla pods and hand- pollination of approximately 40,000 flowers.[11] Madagascar and other island nations in the Southwest Indian Ocean (Comoros, Réunion) historically account for around three quarters of the world's vanilla bean production–and continue to dominate the market today. Vanilla bean production and processing is a vital cash crop in agroforestry systems where there are few alternative income sources.

In Madagascar, an estimated 80,000 families cultivate vanilla orchids on approximately 30,000 hectares. In Comoros, about 5,000-10,000 families depend on vanilla bean production. Approximately 10,000 farm families in Mexico cultivate vanilla orchids, the geographic center of origin of vanilla.[12]

The vanilla cropping system in these countries is vital for the maintenance and sustainability of agroforestry areas (mainly organic). The vanilla orchid vines rely on tropical forest shade and support, and require labor-intensive cultivation, harvest and processing. About 8,000 families in Central Africa (Uganda, Democratic Republic of Congo, Tanzania) depend on vanilla bean production. In recent years Indonesia and China have become major vanilla bean producers; other vanilla bean producers include French Polynesia, Malawi, Tonga, Turkey and India.

Current R&D

In 2009 researchers working with Switzerland- based synthetic biology company, Evolva, described the creation of a de novo pathway to produce vanillin from glucose in two yeast strains; a pathway involving bacterial, mold, plant and synthetic versions of human genes.[13]

• 2010–Evolva enters a 4-year agreement with the Danish government's strategic research council to develop an environmentally sustainable production route for biosynthetic vanillin.

• January 2011–Evolva and International Flavors & Fragrances (IFF) launch partnership to commercialize a biosynthetic route for production of vanillin.

• February 2013–Evolva and IFF announce they are scaling up production of biosynthetic vanillin and "on-target" to launch commercially in 2014.

The commercial success of biosynthesized vanillin ultimately depends not just on competitive price and flavor, but labeling.

In 2009 the global vanilla/vanillin market, including natural, synthetic and artificial sources, was valued at approximately $650 million. Evolva believes that its fermented vanillin can capture up to $360 million of the total global market.[14]

The company's yeast-based fermentation route is producing vanillin at a price that is competitive with the most expensive artificial vanillin on the market today.[15] According to Evolva CEO Neil Goldsmith: "99% of the vanillin that we all eat comes from petrochemicals or chemically treated paper pulp. If we can offer an alternative that is more sustainable and higher quality then we believe that to be beneficial."[16]

Evolva acknowledges that the flavor of the company's biosynthesized vanillin is not equivalent to the flavor-

Real or Artificial?
Flavor & Fragrance Industry Pledges Corporate Commitment to Sustainable and Ethical Sourcing of Vanilla

International Flavors & Fragrances: Within months of announcing that it is "on target" to commercialize its biosynthetic vanilla, IFF released its 2013 sustainability report, pledging the company's commitment to "Natural Ethics Vanilla"– the purchase of vanilla from farmers who adhere to strict sustainability guidelines.20 IFF wants to ensure that the farmers who supply the company's natural vanilla beans are using sustainable production practices. But the company is simultaneously bankrolling (and claiming monopoly patents on) the development of a new biosynthetic process that will potentially disrupt or destroy the livelihoods of hundreds of thousands of small-scale farmers–literally overnight.

Givaudan: "The sustainable sourcing of raw materials is an integral part of our operations and is one of our strategic pillars as well as being part of our Sustainability programme." Our ethical vanilla sourcing programme in Madagascar involves improving traceability, helping farmers certify their organic produce and supporting school building projects."[21]

Firmenich: Firmenich has begun commercializing Bourbon vanilla that has been sourced from Rainforest Alliance CertifiedTM farms. Firmenich has worked with a local partner in Madagascar to help a vanilla bean co-operative of more than 1,300 farming families from 38 villages earn Rainforest Alliance certification.[22]

Intellectual Property Related to Biosynthesis of Vanilla

Company	Patent/Application #	Title	Date Published
International Flavor & Fragrances/Evolva	WO2013022881 A8 (application)	Composition and Methods for the Biosynthesis of Vanillin	21 March 2013
Evolva SA	US8105786	Method of producing a low molecular weight organic compound in a cell	31 Jan 2012
Evolva SA	EP2388333A3	Method of producing a low molecular weight organic compound in a cell	4 April 2012

ing derived from the cured vanilla bean, but claims that the taste profile of vanillin produced by engineered yeast is more complex and closer to the natural vanilla flavor than artificial vanillin.[17] The commercial success of biosynthesized vanillin ultimately depends not just on competitive price and flavor, but labeling. Will IFF's customers–the food companies that use vanillin in bakery/confectionary /dairy/beverages–be permitted to label a biosynthesized vanillin ingredient as "natural"? IFF's director of R&D recently told the *New York Times,* "The need for natural is the key driver."18 Recent precedent suggests that biosynthesized vanillin produced via fermentation may win the natural label: Chemical giant, Solvay (Belgium), already makes a vanillin ingredient via fermentation of ferulic acid derived from rice bran. Government regulators permit Solvay's bio-fermented vanillin to be labeled "Natural flavoring/Flavor/Vanilla flavor" (EU) or "Vanillin derived by a natural process" (US).[19]

Evolva plans to make several molecules involved in the complex flavor profile of natural vanilla. While Evolva insists that its biosynthesized vanillin is not designed to compete with farmer- grown vanilla beans, if the company succeeds in producing a vanillin flavor that can be marketed as "natural" and scaled-up at a fraction of the cost of botanically-derived vanilla, it has the potential to provide a bio-based substitute that will inevitably capture some portion of the natural vanilla bean flavor market.

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20 IFF. 2013. Moving Forward, our sustainability report 2012. http://www.iff.com
21 Givaudan–2012 Annual Report: http://www.givaudan.com
22 Firmenich News Release. "Firmenich Becomes the First Flavor House to Offer Rainforest Alliance CertifiedTM Vanilla," March 27, 2013. http://www.firmenich.com

If Evolva succeeds in producing a vanillin flavor that can be marketed as "natural," it has the potential capture some portion of the natural vanilla bean flavor market.

Vetiver

A SynBio Case Study

photo: Forest and Kim Starr

Product: Vetiver oil, a fragrance widely used in cosmetics and perfumes, is extracted from the aromatic roots of a perennial grass native to India (*Chrysopogon zizanioides)*, commonly known as vetiver.

Status: California-based synthetic biology company, Allylix, Inc., has engineered a metabolic pathway in microbes to produce a key fragrance compound found in vetiver oil. The company had announced plans to launch commercial sale of its biosynthetic fragrance in the third quarter of 2012, but it remains unclear whether the product is currently being sold or not.

Affected Country/Region: Farmers in Haiti, Indonesia, China, Japan, India, Brazil and Réunion grow vetiver for export. In 2007, small farmers in Haiti accounted for an estimated 60% share of worldwide vetiver exports. **Haiti's vetiver crop is processed by 10 distillers, but it provides jobs for some 27,000 farming families in the southwest.** For these farmers, the vetiver plant has important conservation benefits, preventing soil erosion, and helping maintain water quality.

Market: 250 tons *per annum*, worth between **$12 to $16 million.**

Commercialization: Announced for 2012; company has not provided updates since then.[1]

What is Vetiver?

GQ Magazine has called it the "perfect natural raw material for a masculine scent." A distant relation of lemongrass native to India, the perennial vetiver grass (*chrysopogon zizanioides)* is the source of vetiver oil. Known for its musty, woody scent, vetiver oil is also know for its fixative qualities, which means that it helps a fragrance to last longer after it is applied to the skin. Vetiver oil can be detected in the "base notes" of many perfumes or colognes. It is the basis of the Indian perfume "Majmua" and is the major ingredient in some 36% of all western perfumes (e.g. Caleche, Chanel No. 5, Dioressence, Parure, Opium) and 20% of all mens' fragrances.[2] According to U.C. Lavania, a scientist at India's Central Institute of Medicinal and Aromatic Plants, vetiver is used in 90% of all Western perfumes.

> *"a perfect natural raw material for a masculine scent" –GQ*

Annual world trade of vetiver is an estimated 250 tons. Major commercial producers include Haiti, Indonesia, China, Japan, India, Brazil and Réunion. For at least two island nations–Haiti in the Caribbean and Réunion in the Indian Ocean–the essential oil obtained from the roots of vetiver is a major source of foreign exchange earnings. Haiti's share of worldwide vetiver exports grew from 40% in 2001 to over 60% in 2007. In the wake of the worldwide financial crisis, Haiti has seen a sharp reduction in

photo: Victor Wong

vetiver exports. Haiti produces about 50 to 60 tons of vetiver annually, about 50 percent of the world's supply.

An estimated 60,000 people in Haiti's Les Cayes region depend on vetiver as their primary income source; the crop is grown on 10,000 hectares. The region also supports up to 10 distilleries that process and extract vetiver oil for export. Before 2009, Haiti's vetiver crop was valued at approximately $15-$18 million per annum. In recent years, Haiti's export earnings from vetiver have declined to around $10 million per annum.

Current R&D

In March 2012, Allylix, Inc. announced that it would begin commercial sale of a new fragrance that the company calls "Epivone™"–which is structurally related to beta-vetivone, one of the key components of vetiver oil–in the third quarter of 2012. Epivone™ is produced via fermentation. The company estimates that sales of similar terpene molecules used in fragrance applications amount to between $20 and $200 million dollars per year.[3]

With current data, it is not possible to predict how or if Allylix's new biosynthetic product will affect demand for botanically-derived vetiver oil and the livelihoods of small-scale farmers who depend on it.

Conservation Benefits

The the vetiver plant provides vital natural protection against soil erosion and helps maintain water quality. Vetiver has a strong fibrous root system which rapidly penetrates deep into soil, and develops into a tightly-knit net. The vetiver roots holds the soil together and serve as an underground wall which slows water flow. The roots absorb plant nutrients and chemical substances, and protect water sources from chemical fertilizers and pesticides. Farmers also use vetiver to regulate soil moisture, recharge groundwater, recycle soil nutrients and control pests.[4]

For More Information

ETC Group has published several documents explaining and analyzing the impact of Synthetic Biology on biodiversity and livelihoods including *Extreme Genetic Engineering – An introduction to Synthetic Biology*, *The New Biomassters – Synthetic Biology and the Next Assault on Biodiversity and Livelihoods* and *The Principles for the Oversight of Synthetic Biology.* These publications are available on our website: http://www.etcgroup.org/en/issues/synthetic_biology

The Potential Impacts of Synthetic Biology on the Conservation & Sustainable Use of Biodiversity: A Submission to the Convention on Biological Diversity's Subsidiary Body on Scientific, Technical & Technological Advice (A Submission from Civil Society): http://www.etcgroup.org/en/node/5291

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Intellectual Property related to Biosynthesis of Vetiver:

US Patent #: 8,124,811: Fragrance and methods for production of 5-epi-β-vetivone, etc. Assignee: Allylix. Date published: 28 February 2012.

US Patent #: 7,622,614: Methods for production of 5-epi-β-vetivone, etc. Assignee: Allylix. Date published: 24 November 2009.

WIPO Patent #: WO2008116056A2: NOVEL METHODS FOR PRODUCTION OF 5-EPI-β-VETIVONE, etc. Assignee: Allylix, Inc. 25 Sept. 2008.