Synthetic Biology's impact on Livelihoods and Sustainable use of Biodiversity

Pathways To Disruption?

Issue: Due to problems with scale-up, some synthetic biology companies are shifting focus away from biofuels to high-value / low-volume products – especially compounds found in plants (e.g., essential oils, flavours, fragrances, colourants and pharmaceuticals) – which are traditionally cultivated by farming communities in the global South. 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 one synthetic biologist, "We ought to be able to make any compound produced by a plant inside a microbe."[1]

Impact: If commercially viable, synthetic biology's patented organisms have the potential to de-stabilize natural product markets, disrupt trade and eliminate jobs. 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 (i.e., plant cell culture and transgenics) to manufacture high-value natural products were largely unsuccessful. It is too soon to know how well compounds produced through synthetic biology will compete in the marketplace with botanically-derived products; likewise it is difficult to predict which natural products or economies will be most affected and how quickly (see table).

Players: The global market for compounds derived from plants has been estimated at $65 billion.[2] The market for flavour and fragrance compounds alone is over $20 billion *per annum*.[3] 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.

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).
- Artemisia: Currently sourced from Asian and African farmers (~$90 million market p/a).
- 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).

What is Synthetic Biology?

• The design and construction of new biological parts, devices and systems that do not exist in the natural world and also the re-design of existing biological systems to perform specific tasks.

• Sometimes referred to as "extreme genetic engineering," synthetic biology's aim is to converge molecular biology, computing and engineering.

Syn Bio's Plan B: Biosynthesis of Natural Plant Products

For the past five years, synthetic biology enthusiasts have wooed public and private investors with the promise that industry's designer organisms will end dependency on fossil fuels. In 2010, the founder of Synthetic Genomics, Inc., Craig Venter, told *The New York Times*: "Designing and building synthetic cells will be the basis of a new industrial revolution…The goal is to replace the entire petrochemical industry."[4] With the initial focus on biofuels, synthetic biology attracted billions of dollars in public and private funding, including investments from the world's biggest energy and chemical firms (BP, Royal Dutch Shell, Chevron, ExxonMobil, Total, Valero, DuPont, etc.).

But there has been a recent and sudden shift in synthetic biology's business plan. While not abandoning the technology, companies like Amyris, Inc. are acknowledging they can't produce biofuels in volumes competitive with fossil fuels.[5] Profits will come sooner, they think, from the biosynthesis of natural plant compounds using metabolic pathway engineering.

There's nothing new about industry's quest to find cheaper, more abundant and easily accessible supplies of high-value raw ingredients that originate in the tropics and sub-tropics. Over the past 25 years, supplies of many plant-derived compounds may be limited or unstable due to vagaries of weather, political/labor problems or the difficulty of extraction far from industrial processing facilities. Companies have focused on the same goals using other new technologies – with limited success.[6]

What is metabolic pathway engineering?

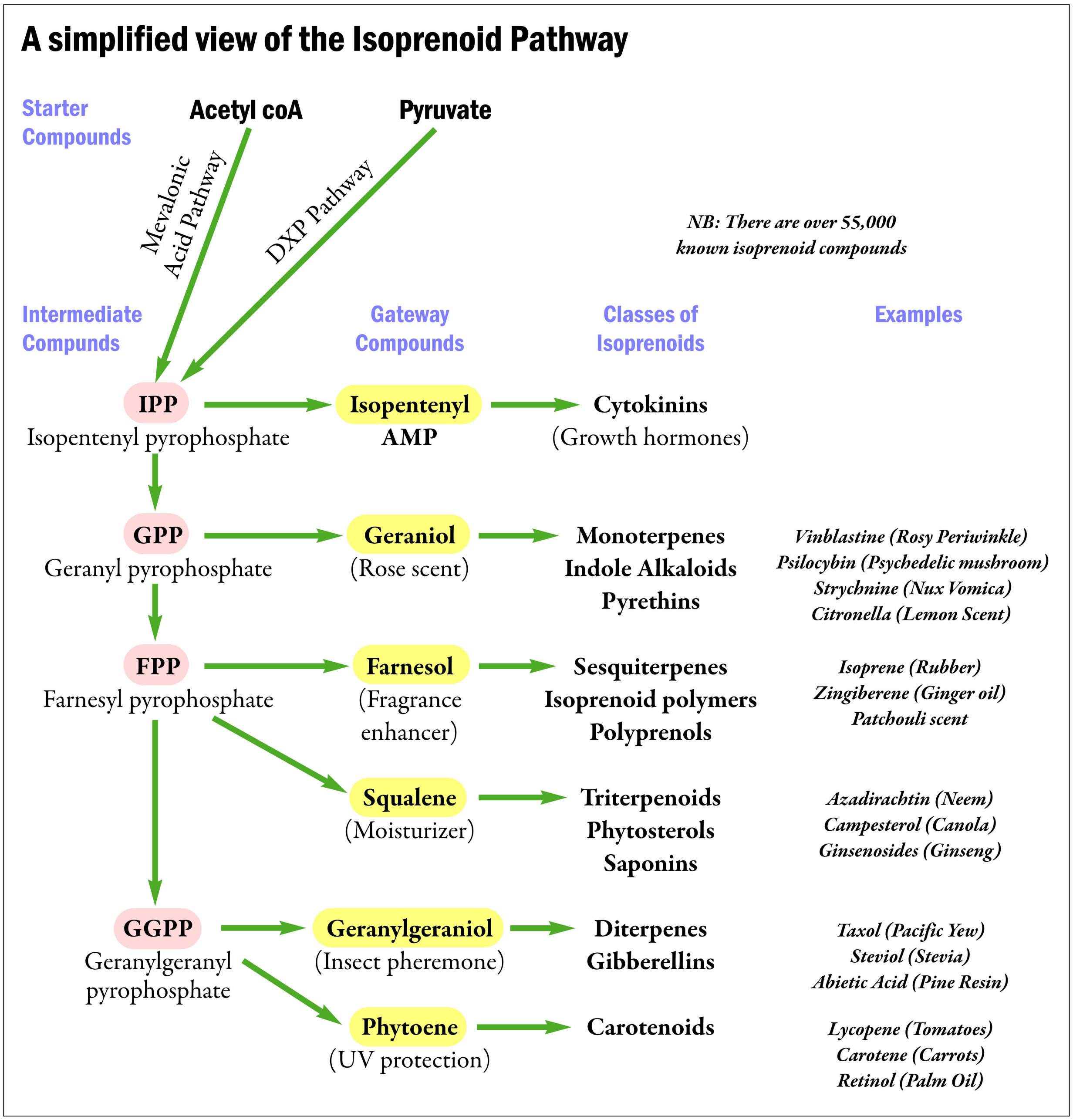
A metabolic pathway describes a series of chemical reactions that take place within a cell that results in a chemical compound. An initial 'starter compound' produced in the cell is chemically altered by the production of different enzymes (plant proteins) in a particular sequence leading to a final compound known as a 'secondary metabolite.' At each step along the pathway, different genes or sets of genes are responsible for producing the specific enzymes that regulate the cell's internal chemistry. The full set of these step-by-step genetic instructions is described as the 'metabolic pathway.'

Synthetic biologists seek to engineer these pathways in order to regulate or change the metabolite that is produced. New metabolic pathways are built from scratch using synthetic DNA and then they are 'optimized' to increase yields of desired, high-value metabolites. Inserted into microbial hosts, the foreign pathways change the way the hosts metabolize plant sugars, so that fermentation tanks can become production facilities for high-value compounds.

Based on current understanding, just eight major 'metabolic pathways' may lead to almost all known plant compounds, totaling around 200,000. In plants, each of these major metabolic pathways begins with one of twelve precursor molecules that are produced in both microbial and plant cells alike.[7] Synthetic biology companies are now systematically working to build these key metabolic pathways into microbes for fermenting commercial products.

BIOSYNTHETIC ISOPRENOID PRODUCTION: MONOPOLIZING 55,000 COMPOUNDS?

Two of the eight pathways (the mevalonate pathway and the DXP pathway) comprise two possible routes to biosynthetic production of the 55,000 known isoprenoid compounds. Commercially valuable natural isoprenoid products range from Isoprene (rubber) to citronella (lemon fragrance), from psilocybin (a compound in 'psychedelic' mushrooms) to taxol (an anti cancer drug from yew trees), from ginsenosides (stimulant compounds in ginseng) to Azadirachtin (antibacterial compound in neem) to zingiberene (the flavour of ginger) and much more.



Isoprenoid pathways have been successfully constructed in yeast and *E. coli*. Engineering the isoprenoid pathway to capture natural-product markets is already the business plan for a handful of synthetic biology companies – notably Amyris (USA), Allylix (USA), and Evolva (Switzerland).

Ultimately, government regulations of commercial biosynthetic products will depend on how compounds are marketed – for example, as flavours, food ingredients, pharmaceutical compounds or insecticides. If synthetic biology companies are able to convince regulators that their bio-synthetic products are 'natural' or 'substantially equivalent' to the botanically-derived counterpart, it will give a major advantage to products manufactured in cell 'factories' via fermentation. If biosynthesis of natural products can be successfully scaled-up, the food, cosmetics and pharmaceutical industries may source future supplies of natural plant products from synthetic microbial cell factories instead of farmers in Asia, Africa and Latin America.

THE NEW AND EMERGING ISSUE OF SYNTHETIC BIOLOGY REQUIRES URGENT ATTENTION BY SBSTTA

No inter-governmental body is addressing the potential disruptive impacts of synthetic biology on developing economies, biodiversity and livelihoods. The Convention on Biological Diversity is the appropriate forum to address this new and emerging issue.

WE RECOMMEND THAT SBSTTA PROVIDE THE FOLLOWING ADVICE TO COP11:

Parties to the Convention on Biological Diversity, in accordance with the precautionary principle, should ensure that synthetic genetic parts and living modified organisms produced by synthetic biology are not released into the environment or approved for commercial use until there is an adequate scientific basis on which to justify such activities and due consideration is given to the associated risks for biological diversity, including socio-economic risks and risks to the environment, human health, livelihoods, culture and traditional knowledge, practices and innovations.

Biosynthesis of Natural Plant Products in Engineered Microbes – Examples

Natural Compound	Institution/Firm Developing Synthetic Biology Production	Stage of Development	Natural Product Source	Market Size (Estimated)	Intellectual Property Claims
Commercial Products					
Star Anise (shikimic acid, key raw material in the anti-viral drug oseltamivir, a. k. a. Tamiflu)	Roche contracts with Sanofi-aventis (France) and others for the microbial production of shikimic acid via fermentation	Most of the shikimic acid used by Roche for Tamiflu comes from microbial fermentation	China	Worldwide sales of Tamiflu fluctuate: 2009 sales $2,954 million; in 2011 $406 million	US8080397 (family of 14 patents and applications) US7790431 US20120052547A1
Squalene (natural moisturizer)	Amyris, Inc.	Commercial production via engineered yeast began in 2010	Previously harvested from livers of deep-sea shark, but can also be efficiently sourced from olive oil and other plants	Global market for squalene is 1,000-2,000 tons per year.	US7691792 WO2010115097A2 WO2010042208A2
Nootkatone, (grapefruit fragrance) and valencene (orange fragrance)	Allylix, Inc. (USA)	In commercial production via microbial fermentation since 2010	Natural citrus peels (grapefruit and orange)	Potential flavor/fragrance market for terpenes and derivatives ~$650 million	Allylix claims its proprietary platform protected by 57 patents
Near-term commercialization					
Artemisinin (*Artemisia annua)*	Amyris / Sanofi-aventis; Riken Institute	Trial batches may be available from Sanofi-aventis by the end of 2012	China, Vietnam, Cameroon, Ethiopia, Kenya, Mozambique, Tanzania, Uganda and Zambia	Global artemisinin demand in 2012 is ~185 MT; Price: $650/kg in Oct. 2011	US8101399 US7622282 US7192751 US7172886
Isoprene from Natural Rubber (*Hevea brasiliensis*)	Amyris/Michelin; Genencor/Dupont (USA) Goodyear Tire & Rubber Co.; GlycosBio/ Bio-XCell Sdn Bhd (Malaysia)	BioIsoprene to be commercialized 2013 (Genencor/ Goodyear) or 2014 (GlycosBio)	Thailand, Malaysia, Indonesia, India, Vietnam, China, Sri Lanka, Cambodia, Papua New Guinea, Philippines	8.9 million MT (demand for isoprene *per annum*)	US7803985 EP2281890A1 WO2010148150A1 WO2011079314A2 WO2010031062A1 WO2009042070A2
Saffron (*Crocus sativus, L.*)	Evolva, Inc. (Switzerland)	R&D initiated in 2010 – possible product in 2015 or 2016.	>90% from Iran; Spain, India, Morocco, Greece, Turkey, Kashmir, Afghanistan	$660 million *per annum*. Price: >$ 2,000 per k.	EP1472349B1 EP1364005B1 WO2011146833A1
Vetiver Oil (*Chrysopogon zizanioides)*	Allylix, Inc. (USA)	Commercial product to be launched in 2012	Native to India; Commercial producers are Reunion, Haiti, Indonesia, China	$10 million in Haiti alone	US8124811 US7622614 WO2008116056A2

Natural Compound	Institution/Firm Developing Synthetic Biology Production	Stage of Development	Natural Product Source	Market Size (Estimated)	Intellectual Property Claims
LONGER-TERM R&D ON BIOSYNTHESIS OF NATURAL PLANT PRODUCTS					
Licorice (*Glycyrrhiza glabra)*	RIKEN Institute, Tokiwa Phytochemical Co. (Japan)	Proof of principal	India, Spain, Iraq, Iran, Turkey, Russia, China, Mongolia, Kazakhstan	Licorice trade valued at ~$42 million (2007)	N/A
Berberine or Zereshk (*Berberis vulgaris*) Spice and medicinal plant	California Institute of Technology	Proof of principal	Iran is world's largest producer	N/A	N/A
Opium Poppy *(Papaver somniferum)*	PhytoMetaSyn (Canada); GlaxoSmithKline (UK)	Identification of genes/enzymes that enable the opium poppy to make codeine and morphine	Tasmania	N/A	WO2011058446A2 WO2012010872A2
Pyrethrum (*Tanacetum cinerariaefolium)*	Wageningen University (Netherlands); Dainihon Jochugiku Co., Ltd., Yamaguchi University, Kinki University (Japan)	Current R&D seeks to synthesize genes for breeding *T. cinerariifolium* cultivars with enhanced pyrethrin production	Kenya, Australia, Tanzania, Rwanda, China	East Africa traditionally largest pyrethrum producer; ~200,000 Kenyan farmers grow pyrethrum valued at up to $135 million.	N/A
Prostratin (*Homalanthus nutans*) Source of anti-viral compounds	Lawrence Berkeley National Laboratory (USA)	Jay Keasling's lab supports small R&D program; in 2008 prostratin produced via synthetic chemistry	Samoa	Not yet approved for drug use	N/A
Resveratrol (compound derived from various plants valued for health benefits)	Scientists associated with Riken (Japan); Danforth Center and Monsanto (USA); Chinese Academy of Sciences and others	Proof of principal; metabolic engineering of Resveratrol achieved in plants, microbes and animals	Japanese knot weed (*Polygnum capsidatum*), a traditional medicinal plant; dietary sources include grape (*Vitis sp.*), peanut (*Arachis hypogaea*) and several berry varieties.	N/A	YES
Stevia (*Stevia rebaudiana)*	Evolva, Inc. (Switzerland), Vineland Research (Canada)	Pre-commercial, R&D; 2015 commercial target date	Paraguay, Brazil, Argentina Uruguay, Israel, China, Thailand, United States	Worldwide sales of Stevia extract 3,500 tons (2010); market for high-intensity sweeteners: $1.2 billion	WO2011153378A1 US8062878

Natural Compound	Institution/Firm Developing Synthetic Biology Production	Stage of Development	Natural Product Source	Market Size (Estimated)	Intellectual Property Claims
Taxol *(Taxus brevifolia)* Pacific yew tree, source of anti-cancer compounds	MIT and Tufts University (USA); Fraunhofer Institut für Molekular-biologie und Angewandte Ökologie; Forckenbeckstrae Institut für Organische Chemie und Biochemie, Technische Universität (Germany)	Pre-commercial; taxol precursor produced in *E. coli.* Taxol already being manufactured by Bristol Myers Squibb via plant cell culture	USA/Canada	Worldwide sales of paclitaxel (generic Taxol) $459 million in 2010. Sales of top 5 drugs containing paclitaxel $3,200 million in 2011	US20110189717A1
(*Catharanthus Roseus*) Source of ~70 alkaloids, including anti-cancer vinblastine and vincristine.	MIT (USA); John Innes Center (UK) (Note: The periwinkle plant is being used as the producing organism instead of microbes)	R&D	Madagascar, China, India, Israel	~1000 tonnes exported from Madagascar *per annum* (FAO, 2003)	N/A

SOURCE: ETC GROUP

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/syn

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

REFERENCES

[1] Specter, M. "A Life of Its Own: Where Will Synthetic Biology Lead Us?" *New Yorker*, 28 September 2009. The author is quoting University of California-Berkeley synthetic biologist, Jay Keasling.

[2] This is a 2006 estimate: http://www.irgltd.com/Resources/Discussion_Forum/DF27%20Natural%20Products%20-%20web.pdf.

[3] Hansen, E.H., B. L. Møller, G. R. Kock, C. M. Bünner, C. Kristensen, O. R. Jensen, F. T. Okkels, C.E. Olsen, M. S. Motawia, and J. Hansen, "De novo biosynthesis of Vanillin in Fission yeast (*Schizosaccharomyces pombe*) and Baker's yeast (*Saccharomyces cerevisiae*)," *Applied and Environmental Microbiology* 75, 2009, pp. 2765-2774.

[4] Andrew Pollack, "His Corporate Strategy: The Scientific Method," *New York Times*, 4 Sept 2010.

[5] http://www.technologyreview.com/blog/energy/27570/

[6] In 1987 ETC Group (then as RAFI) first warned of possible impacts of plant cell culture for vanilla and pyrethrum producers, for example. The companies were not commercially successful. However, Bristol Myers Squibb is commercially producing anti-cancer compound Taxol using plant cell culture. See http://www.etcgroup.org/upload/publication/556/02/raficom25vanillaupdate.pdf.

[7] Nielsen, J., "It is all about metabolic fluxes," *J Bacteriol* 185, 2003, pp. 7031–7035.