Biotechnology Enters Its Next Phase

Recent ingredient launches signal increasing complexity of biotechnologically derived natural flavor and fragrance materials.

"Biotech flavors could replace some natural flavors, being manufactured within a controlled environment at a lower cost," notes a recent UBIC Consulting (*www.ubic-consulting.com*) report. "They can also replace some nature-identical flavors and justify a natural label."

Indeed, flavor and fragrance industry investments in biotechnology-derived ingredients has ramped up in recent years, reflecting a recognition of potential advantages compared to some conventional counterparts, including: affordability, availability, efficiency of production and low environmental impact.

Natural Preference in Fragrance and Flavors

Consumers' growing preference for natural products is nothing new, but it is increasing.

"One-third of consumers say they 'prefer personal care products made with natural or organic ingredients,' including 25% of men and 38% of women," notes a recent Kantar (*http://us.kantar.com/*) report.

The report adds that the preference, depending on age range, is as high as 43% and 33% for women and men, respectively.

Meanwhile, in the home care arena, a 2013 Mintel (*www.mintel.com*) report explains, "64% of consumers said they would buy more eco-friendly products if they were less expensive." This attitude has been accompanied by a push by major retailers such as Walmart and Target into the natural household and personal care space.

A Packaged Facts (*www.packagedfacts.com*) report that tracked the growth in the U.S. natural household surface cleaner and laundry product market concluded that retail sales rose from $303 million in 2007 to $640 million in 2011.

The report adds, "Correspondingly, 41% of respondents to an online Packaged Facts consumer survey conducted in August 2012 indicated that they had purchased or used natural, organic, or eco-friendly household cleaning/laundry products within the previous 12 months, up from 38% in February 2009."

Simultaneously, consumer attitudes toward natural flavors continue in a similar direction.

According to a 2013 DSM (*www.dsm.com*) survey of Nigerian, U.S., Chinese, Polish and Brazilian consumers, "more than half (55%) believe a 'fresh or natural' flavor is what makes food taste delicious, followed by 'tastes as if it was made at home.'"

A new Evolva partnership will begin with the yeast fermentation production of agarwood fragrances; agarwood image via Creative Commons.

Firmenich has scaled up production of a woody patchoulilike fragrance molecule.

Interestingly, the report added, "This was felt most strongly by urban consumers living in China (72%), while their counterparts in Brazil said they first and foremost wanted food that 'tastes as if it were made at home' (67%)."

The DSM report concluded, "These cravings for fresh, natural or homemade tastes is one of the more important challenges for food producers in the face of consumer behavior, as

Further Reading: Biotech Ingredients In Use

Dec-9-en-2-one, produced via biotechnology and commercialized by Mane under the Antillone trade name, is profiled by flavorist John Wright, who discusses its use in tropical fruit, berry, citrus and other flavor profiles. Read more on Page 16 of the May 2014 issue of *P&F*, *www.perfumerflavorist.com/magazine/pastissues/*.

Evolva is expected to launch a biotechnology-derived saffron product in 2016.

nearly two-thirds (64%) of urban consumers report they are using the same amount of or more processed food at home than they were three years ago."

Consequently, it is no surprise that a Markets and Markets (*www.marketsandmarkets.com*) report forecasts that the global natural flavors market will be worth $5 billion by 2017. (Research and Markets [*www.researchandmarkets.com*] predicts that the global flavor industry—natural and synthetic—will total $13 billion by 2018.) *Reportsnreports.com* places the growth of the natural flavor and color market at a compounded annual growth rate of 6.35% through 2018.

Research and Markets explains, "[O]ne of the main drivers in this [food and beverage] market is the increase in the demand for food products that contain natural flavors and colorants. This demand has resulted from the growing health-conscious population seeking to consume food and beverage products that have natural labels on the pack, as they consider them to be safer and healthier."

Nootkatone & Valencene

The UBIC Consulting report details several ingredients that are obvious targets for biotechnology production, including vanillin, furaneol, raspberry ketone and nootkatone. Many, if not all of these, have already been pursued commercially.

For example, DSM Nutritional Products Ltd. (Heerlen, the Netherlands) has formed an exclusive partnership with Isobionics B.V. (Geleen, the Netherlands) to distribute valencene and nootkatone to the flavor and fragrance market. The materials, intended to address price stability and supply reliability issues, will be produced via Isobionics' fermentation technology. (Isobionics' "valencene synthase" is detailed in WIPO patent application WO/2011/074954, which comprises "converting farnesyl diphosphate to valencene in the presence of a valencene synthase.")

"The current supply chain of many natural compounds is unstable and characterized by high volatility regarding availability, quality and pricing," said Toine Janssen, CEO and founder of Isobionics. "With our proprietary fermentation technology, which is similar to brewing beer, we create the stability and reliability of supply that the market expects."

The DSM-Isobionics announcement follows the earlier large-scale valencene production initiated by Allylix (San Diego), which began producing "commercial quantities" of

the material in 2011. The ingredient was intended for application in beverages, confectionery and over-the-counter health care flavors.

Allylix commercialized nootkatone in early 2010, based on the firm's patented metabolic engineering platform, which enables low-cost production of high-value terpene products and terpene derivatives through yeast fermentation. The production of large-scale commercial quantities is made possible by 200,000-l fermentation tanks. In 2012, the company also released its Epivone[a] brand terpene, epi-β-vetivone, for fragrance applications. The material has a scent that is reportedly woody, vetiver, cassis and fruity, with a grapefruit effect. The ingredient can have 500-hour substantivity on the blotter and is applicable in cologne, hair care and personal care fragrances. At the time of the announcement, the company noted that annual revenue for similar terpene molecules used in fragrance applications is estimated between $20 million and $200 million.

According to the Lexington Herald-Leader, Allylix has secured incentive financing for a reportedly $1.63-million laboratory expansion in Kentucky for its flavor and fragrance and other product activities. It has also secured a U.S. patent (8,642,815) for the use of premnaspirodiene as a starting material for the production of "5-epi-β-vetivone, 2-isopropyl-6,10-dimethyl-spiro[4,5]deca-2,6-dien-8-one and 2-isopropyl-6,10-dimethylspiro[4,5]deca-1,6-dien-8-one, which are useful for their fragrant qualities." It has also secured a U.S. patent (8,753,842) for a "method for production of isoprenoid compounds."

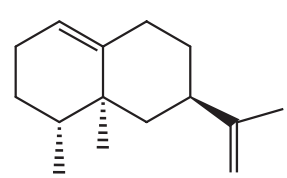
Patchouli & Beyond

Elsewhere in the biotech space, Firmenich has scaled up production of a woody patchoulilike fragrance molecule, Clearwood[b], from the fermentation of sugar cane, at a Brotas, Brazil, facility. The ingredient debuted at the 2014 *World Perfumery Congress* (see **Page 60** for coverage).

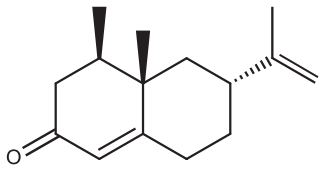
"This technology will enable Firmenich to make differentiated perfume creations with unique renewable ingredients," said Boet Brinkgreve, group vice president, ingredients at Firmenich. "Our clients expect reliability of supply, cost innovation and olfactive differentiation, all of which we think the move to Brotas will help support."

Amyris and Firmenich are working on the production of additional molecules intended for the flavor and fragrance industries, according to the companies. They will share the "economic value derived from the sale of these ingredients," according to an official press release. These terms are part of an expanded collaboration agreement for the development and commercialization of flavor and fragrance materials. Existing Amyris agreements with other industry players excepted, Firmenich has exclusive access to the Amyris technology platform for the flavor and fragrance market in exchange for "significant funding over the next six years."

"Innovation and sustainability are critical pillars of our business model," said Firmenich CEO Patrick Firmenich. "We are very pleased with the progress of our ongoing collaboration with Amyris, grounded in our vision to be the leaders in renewable ingredients for the flavor and fragrance market."



Valencene can be produced via biotechnology.



Nootkatone can also be produced via biotechnology.

"We are excited to expand our productive collaboration with Firmenich," said John Melo, Amyris' president and CEO. "The rapid pace of our targeted ingredient development so far confirms our ability to deliver a host of disruptive, competitive ingredients to our partners and underscores the strategic value of collaborations for Amyris."

Rob Stone and James Medvedeff of Cowen & Co., quoted by BiofuelsDigest (*www.biofuelsdigest.com*), estimated that Amyris is currently working with five partners in the flavor and fragrance space, comprising the development of as many as 22 molecules.

Farnesene-derived Materials

Amyris is also focused on producing fragrance materials from farnesene. The company previously ramped up its production of artemisinin and the renewable hydrocarbon farnesene, the latter of which is produced under the company's Biofene brand name. The company recently announced a partnership with Takasago (Tokyo) to commercialize novel fragrance products derived from farnesene, following successful feasibility testing that began in 2012. Scale-up is already underway. The ingredients will reach the market in 2015.

"The use of Amyris' renewable farnesene supports Takasago's goal of utilizing innovative, cost-effective and sustainably sourced materials to make products that impact our customers' daily lives," noted Masayuki Mita, senior vice president of the fragrance and aroma chemical division at Takasago. "These new products will address customer demand resulting from the regulatory phase-out of certain existing fragrance ingredients, and will be some of the newest and most valuable fragrance ingredients on Takasago's palette."

Zanna McFerson, chief business officer at Amyris, said, "Takasago's strong scientific and manufacturing expertise is expanding the range of new fragrances made possible through our innovative technology. We look forward to the commercialization of these products and to the expansion of the portfolio of products enabled by our building block molecule. The new fragrance ingredients should help our partner extend the impact of their products on the diversity of fragrance formulations that perfumers can reach."

Amyris' Brazilian farnesene plant, which is adjacent to a sugarcane mill, has surpassed a production run rate of 1 million liters over a 45-day period, with all six fermenters running. In addition to aromatic ingredients, the farnesene will be applied to renewable diesel and jet fuels and cosmetic ingredients. Another farnesene producer, Intrexon, is producing the building block chemical via bioconversion of natural methane. The company serves the cosmetics and specialty chemicals sector, as well as diesel fuels and lubricants.

[a]Epivone is a trade name of Allylix.
[b]Clearwood is a trade name of Firmenich (read the story of Clearwood on Page 60 of this issue).

Materials Entering New Development Phase

Amyris has also met a technical milestone in the first phase of development for renewable flavor and fragrance ingredients for IFF (New York).

"This arrangement supports our long-term strategy, which focuses on both innovation and portfolio maximization," said Nicolas Mirzayantz, IFF's group president, fragrances. "In our 125-year history, we have been market leaders in the area of innovation, and this recent work with Amyris reflects our continuing commitment to lead in this area. We believe that the creation of cost-effective molecules will have a positive impact on our fragrance ingredients business as well as the creative capabilities of our fragrance compounds business."

Under the terms of the multi-year agreement, IFF has exclusive rights to the renewable fragrance ingredients developed for applications in the flavors and fragrances sector, and Amyris will have exclusive rights in other sectors.

Vanillin, Saffron & Stevia

Evolva Holding SA (Reinach, Switzerland) has announced that it is commercially launching its vanillin, following a successful pre-production phase. The company has collaborated on yeast-based fermentation routes in this area with IFF.

Evolva's stevia products, which will target reduced-calorie formulations, will likely launch in 2015 or 2016. The company began that collaboration, focused on fermentation-based steviol glycosides, with Cargill in 2013. This year, the project reached a technical milestone; as a result, Cargill made a $1-million milestone payment to Evolva. These payments could total as much as $7.5 million in the R&D period.

"We are encouraged by this project's trajectory," said David Henstrom, Cargill's global business director for health ingredients. "We look forward to offering cost-effective, great tasting, minor steviol glycosides in the market in the near future."

A saffron product offering will launch in 2016. The work, conducted at Evolva's site in Chennai, India, is focused on optimizing the sensory and cost profile of the products.

According to the company, "Evolva currently intends to commercialize saffron ingredients in its own right, though it will work with distributors, etc., in a similar manner to resveratrol."

Meanwhile, Evolva has discontinued a collaboration with IFF to produce an undisclosed flavor ingredient. That partnership began in 2012. Evolva's work on the material may continue independently.

Agarwood

Evolva, in cooperation with BiotechCorp, has also entered into a collaboration with the Universiti Malaysia Pahang (UMP) to establish a Malaysian natural product center of excellence in the region's flavor and fragrance cluster. The aim is to apply Evolva's yeast fermentation production platform to indigenous natural products for flavor and fragrance, cosmetic, pharmaceutical and other sectors.

The collaboration will begin with the yeast fermentation production of agarwood fragrances, which the partners hope will "complement the existing traditional production approaches" and "significantly widen" the use of agarwood scents worldwide. Because the *Aquilaria* and *Gyrinops* varieties are endangered, they fall under the Convention on International Trade in

Endangered Species of Wild Fauna and Flora (CITES). Despite this, the global supply of agarwood verges on extinction.

"If successful, this center's global and multi-disciplinary efforts will produce both positive economic and environmental benefits for us all," said Evolva CEO Neil Goldsmith.

"Malaysia has abundant natural products with high potential to be developed into high purity, as well as active ingredients for the cosmetic, pharmaceutical, and other high-end industries," said BiotechCorp CEO Mohammed Nazlee Kamal. "This will create value for other industries with significant economic opportunities to benefit Malaysia's bioeconomy agenda."

Renewable Flavor, Fragrance & Cosmetic Ingredients

Symrise (Holzminden, Germany) and P2 Science (New Haven, Connecticut) have entered a partnership to produce "a slate" of renewable ingredients. The partners will scale up the production of "products of immediate commercial interest" for commercialization over the next year.

The ingredients will be produced by converting biomass into specialty chemicals via ozonolysis. Targeted materials include sustainable versions of existing ingredients and novel aromatic molecules. Novel materials will undergo performance, toxicology and economic feasibility screening. The ingredients that qualify for commercialization will offer Symrise differentiation and improved sustainability.

P2 has also entered into a renewable F&F molecule development agreement with Bedoukian (Danbury, Connecticut). Materials of "commercial interest" will be identified and scaled up to commercial production levels over the coming year.

This year, Amyris scaled up production of a fragrance molecule, produced from the fermentation of sugar cane, at its Brotas, Brazil, facility (pictured). Source: Amyris

"P2's unique chemical process technology for the manufacture of chemicals from biomass is a good fit with Bedoukian's synthesis and separations technology," a P2 statement notes. "As part of the agreement, the companies will evaluate the potential for a joint manufacturing installation to serve the F&F market."

In addressing existing supply and sustainability challenges and offering potentially novel aromatic profiles, biotechnology investments will likely continue to increase in coming years.