

Biotech Terpenes

A cost-effective, high-purity process emerges for natural terpenes

Using emerging biotech processes, one large fermentation tank will be able to produce as much valencene as a pile of oranges standing 500 feet tall and weighing 1 million metric tons. “I think that pretty well illustrates where the scalability and cost-effectiveness comes in,” says Richard Burlingame, vice president of R&D at Allylix, a San Diego-based company that has begun creating and marketing terpenes for the flavor and fragrance industry.

More than 50,000 types of terpenes have been discovered to date, yet most occur in plants and microorganisms at minute levels. And so, says Allylix president and CEO Carolyn Fritz, natural extraction has been markedly expensive. “The alternative technology is chemical synthesis,” she says. “[Terpenes] are typically complex cyclic compounds that are very difficult to synthesize. These chiral compounds typically have three or four chiral centers [R/S], so if you’re trying to create a single isomer through chemical synthesis, that’s very expensive. The value of [creating terpenes] biologically, working with an organism in a fermentation approach, is that they produce a single isomer very efficiently.” In addition, synthetic materials cannot be claimed as natural, which can be a challenge in a consumer environment that increasingly demands natural products.

The Path to Natural Terpene Production

Fritz joined Allylix in 2004, when it was “a single scientist and some glassware,” bringing with her experience garnered from a biotech startup she ran for Cargill in the 1990s, and two businesses—a biochemical/biopolymer operation and a therapeutic protein and antibody contract manufacturer—she built for Dow Chemical. Allylix’s fundraising for the development of a biological approach to terpene production began the following year and moved through three stages, totaling \$15 million. In the meantime, Burlingame came on board, having spent more than two decades as a biotechnologist working with small and large industrial biotech firms, gaining insight into strain development and optimization, amino acid production, metabolic engineering, enzymology, biocatalysis, fermentation, and more.

At the start of its development process, Allylix evaluated potential markets for its terpene products, including pesticides, crop protection, food ingredients,



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pharmaceuticals, specialty chemical applications, and flavors and fragrances. The company chose to initially focus on flavors and fragrances because the compounds it could produce were valuable and because Allylix could get the products to market quickly, compared to the time-intensive development and registration processes of the pharmaceutical and crop protection sectors.

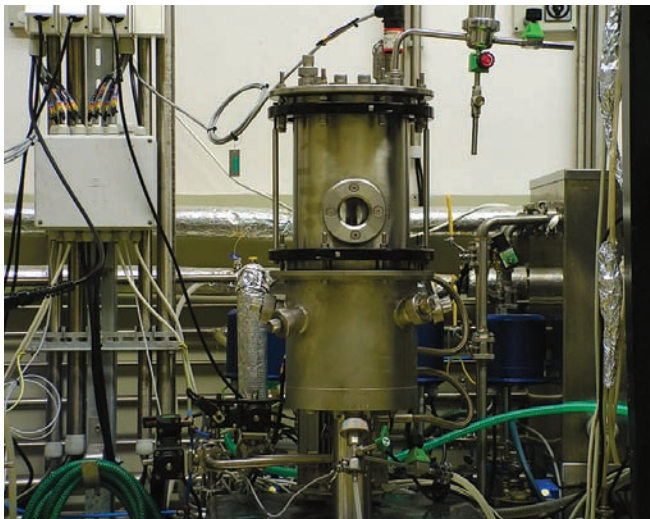
“Longer term, we plan to expand into other markets,” Fritz notes. “We’ve built out a technology platform that is designed to be modular, so now each new product is an incremental investment to develop.”

The Ingredients

“Our key word is sustainable,” says Burlingame. “We can make these products on demand from inexpensive, agriculturally derived raw materials. We’re not isolating them from rare or endangered species. We make them with consistent quality. The current natural products can vary in quality from season to season or year to year, depending on things like weather conditions.”

In vastly simplified terms, the company’s process employs yeast genetically engineered with plant-derived enzyme genes. This combination boosts the yeast’s production of the precursor compound farnesyl pyrophosphate (FPP) and allows that precursor to then be converted into a terpene of commercial interest. “Because the process has been optimized through genetically modifying the yeast, we can produce these compounds at very high yields,” says Burlingame. “Out of a large-scale fermenter we can get multiple tons of product, which if you were extracting it from a natural source would require huge amounts of the starting raw material, whether it be citrus peels or exotic woods or other plant products.”

Fritz notes that the company has so far scaled up and commercialized two products, valencene (FEMA# 3443; CAS# 4630-07-3) and nootkatone (FEMA# 3166; CAS# 4674-50-4). She adds that six additional materials are in



Small pilot scale fermenters such as this one can produce an amount of terpenes equivalent to several tons of oranges.

the development pipeline and will be launched on the market by 2012. At this time the company is not publicly disclosing the identity of the forthcoming ingredients.

“We’re receiving first orders and quite a lot of interest in project work,” says Peter Mueller, vice president of sales and marketing. “Not only is there a reliable supply and lower unit cost [for the terpenes], but we’ve got a very pure product. When you do an extraction of citrus peel, for example, you’re pulling a lot of impurities out with it that are sometimes very difficult to get rid of. So we have an absence of some off notes here.”

Applications

Lowering the cost of terpenes allows for an expansion of their application, Mueller says. “These are products that have been used very sparingly for fine fragrances,” he explains. Expanding the supply of affordable materials, he says, could result in the use of key terpenes in personal and air care applications. “They are currently used in beverages,” Mueller adds, “but this [development] would allow for larger volume beverage brands to utilize the products.” In addition, he says, expanded, reliable and cost-effective supplies of terpenes could extend their use into larger volume SKUs (stock-keeping units) without the worry of “going into year three” with a product that faces ingredient issues due to factors such as natural disasters.

What’s Next?

“Some of the compounds are novel [ingredients] that we have developed through our own libraries,” says Fritz of the six materials currently in the development pipeline. “The others are products that have an existing market that we are going to address. Beyond that we have some ongoing partnering discussions where we will be working with third parties to develop proprietary products for them. Not only will we bring our own products to market, but we’ll be working with third parties to develop products on their behalf.”

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