Taste Receptor Research and the Discovery and Development of New Flavor Materials

Bringing novel materials to market to modulate sweet, salt, umami and cooling sensations

A dire World Health Organization report on the subject of obesity warned, "Overweight and obesity represent a rapidly growing threat to the health of populations in an increasing number of countries. Indeed they are now so common that they are replacing more traditional problems such as undernutrition and infectious diseases as the most significant causes of ill-health."

"We read every day about the link between high levels of sodium in the diet and cardiovascular disease and hypertension," says Mark Zoller, chief scientific officer of Senomyx, a San Diego, California-based company that employs taste receptor-based assays and screening technologies to discover and develop novel flavors, flavor enhancers and taste modulators for the food, beverage and ingredients industries. The company's clients in the arenas of savory, sweet, salt and cooling include Ajinomoto, Cadbury, Campbell Soup Company, The Coca-Cola Co., Firmenich SA, Nestlé SA and Solae. "Similarly, there is concern about high levels of calories and sugar in various foods [due to the world's] growing obesity and diabetes trend," Zoller adds. "Those are some of the key drivers we picked up on. We're responding to an industry that is trying to do more in the health and wellness area."

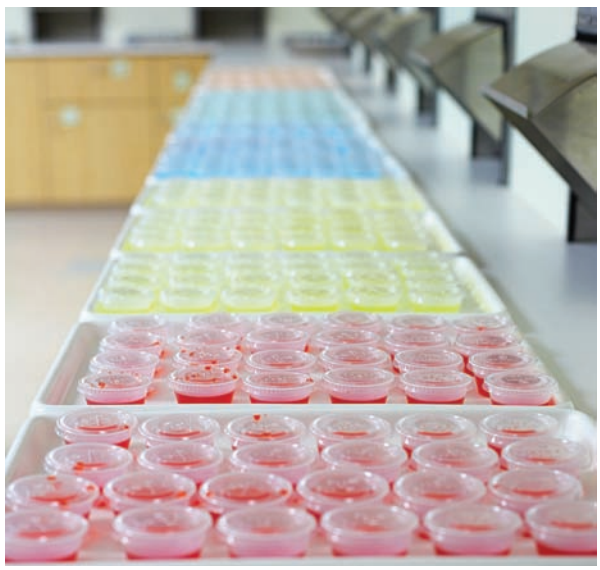
Mark Zoller, Senomyx's chief scientific officer.

Senomyx's background in the biology of taste took shape in the 1990s with a group of founding academics and entrepreneurs, including Charles Zuker, a professor of biology at the University of California, San Diego. "He was studying the biology of taste and had identified what appeared to be the novel receptors that he predicted were going to be involved in taste," says Zoller, "but at the time he hadn't discovered which receptor was responding to which taste." In founding Senomyx, Zuker teamed with a range of researchers, including Lubert Stryer, professor of cell biology at Stanford University and recipient of a 2007 National Medal of Science; Roger Tsien, Nobel Prize-winning scientist and professor of pharmacology, chemistry and biochemistry at the University of California, San Diego (**see sidebar**); food chemistry expert and author of "The Curious Cook" Harold McGee, and Denis Baylor, professor emeritus of Neurobiology at Stanford University. (All remain on the company's scientific advisory board.) "The thought was to use taste receptors to identify novel flavors," says Zoller. "In the beginning, the idea was to work on both taste and smell, but it turned out that the biology of smell is about 100-times more complicated than that of taste. So the focus of the company soon settled down on taste."

Discovery and Development

"The key technology that sets us apart from, say, a traditional flavor house is the use of these receptor-based assays," says Zoller, explaining how the company has over time determined the mechanisms of various receptors. "You could think of it as an artificial taste bud. We know our taste buds have certain cells that respond to many different tastes. What we can do is create a [single taste receptor] system that we can culture and grow in a lab. For example, if we're looking for a sweet receptor enhancer, we can add various samples to the sweet receptor and then only work on the ones that interact or bind to the [relevant] receptor." The company has filed a good deal of patents around this key technology. In addition, Senomyx has developed the technology to acquire the various samples under study. "We have a library of both natural and synthetic samples," says Zoller, estimating the number at around 500,000.

"We learned very quickly that we needed to show that the samples we identified in the receptor were having the



Senomyx's sensory preparation area allows the company to better assess ingredient performance.

desired effect," he continues. "So we then needed to generate a sensory group to be able to study this, much like any flavor house would. In addition, because we needed to see whether these various ingredients functioned in more complex products, we had to develop a product development group. It's not that we'll be developing products for our partners, but we needed to show that the things that we'd identified are heat-stable, soluble and have the required physical properties." The vetted ingredients are then passed along to clients.

"I would argue that we're very complementary to the traditional flavor houses," he says, "because their expertise is in mixing and putting different flavors together. They're really experts in 'how do flavors come together in a flavor mixture, how are they added, what are the various ways in which these products can be manufactured?' We're not trying to compete with the flavor houses. We're discovering new flavors in new ways. Our expertise is really around that discovery process."

Salt and Sweet: Enhancing and Modulating, Not Replacing

"By understanding the biochemistry of the taste receptors, our flavors are basically making them more efficient at what they do," says Zoller. "We're not making a new sweetener in the case of a sweet enhancer and we're not making a salt replacer in the case of a salt enhancer. What we aim to do is modulate or enhance the activity of, say, the salt receptor, making it more efficient so that more sodium flows into the taste cell over a given amount of time. And so, [even] with a lowered amount of sodium, that solution will taste just as salty."

The sweet enhancer program has witnessed two key technical achievements since 2007, namely the discovery, identification and vetting of S6973 and S2383. S6973 reportedly allows for an up to 50% reduction in sucrose without sacrificing the sweet taste of natural sugar. Development activities are already underway. Senomyx views the material as key to good flavors for healthy formulations. Meanwhile, the company is winding down development activities for S2383, which reportedly allows for a 75% reduction in sucralose without off-tastes or loss of sweet intensity.

Tsien Wins 2008 Nobel Prize in Chemistry

Roger Tsien shares this year's Nobel Prize in chemistry for his contributions to the work titled "Wavelength mutations and post-translational autoxidation of green fluorescent protein," published in 1994. Employing a natural tool of some jellyfish, Tsien was able to change the colors of glowing proteins, which allowed them to be tracked during the evaluation of cellular processes. The technique, which has found use in Senomyx's research, has found medical use in the study of Alzheimer's disease.

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In the arena of high-potency sweeteners, the company has screened more than 250,000 natural samples. The goal is to develop novel sweeteners with low or no calories.

Savory/Umami

Senomyx's savory program is its most mature. Its goals, Zoller explains, are two-fold: to replace MSG out of concern for health and cost elements, as well as launching new savory ingredients based on an understanding of savory/umami receptors. "Both of these are being applied in the Nestle product development area," he says. "The flavors are in products. Initially they started in the Pacific Rim and Latin American countries, with the expectation that additional products will be launched over the course of the coming year on a rolling basis."

Blocking Bitter

Senomyx's efforts to improve the healthiness of foods and beverages go beyond the reduction of problem ingredients—they also involve the improvement of the flavor of nutritious, but inherently bitter, ingredients. To this end, the company has partnered with soy protein supplier Solae to block/modulate the bitterness of hydrolyzed soy protein while minimizing the addition of sugar, fat or salt. "It's a very healthy source of protein and could be used to a greater extent if it wasn't for the taste," says Zoller. Solae is betting that these blockers will speed up consumer acceptance of foods containing soy protein, including beverages, energy bars and infant formula. According to the agreement's announcement, "Solae will have exclusive worldwide use of the flavor ingredients in virtually all categories of

Senomyx's electrophysiology screening.

foods and beverages that contain added soy protein. Solae will fund the discovery and development of these flavor systems, and Senomyx will be entitled to certain milestone and royalty payments based on sales of Solae products containing any flavor ingredients developed under the agreement."

Cooling Agents

In many cases, due to confidentiality issues, Senomyx is unable to discuss specifics in terms of which companies are allied with which projects. However, in January of this year Senomyx president and CEO Kent Snyder announced a cooling agent collaboration with Firmenich.

"Annual sales of current cooling compounds are in the $400 million range," he noted at the time. "We estimate the opportunity of flavor systems incorporating approved cooling agents may be three to four times this size."

Under the three-year deal, Senomyx is conducting its taste receptor discovery activities under its Cool Flavor banner, making available any of the resulting (viable) cooling agents to Firmenich, exclusively. Firmenich is paying research fees and additional payments when undisclosed milestones are met. Firmenich will address manufacturing, marketing and sales of any cooling flavor systems.

"Upon commercialization," Snyder noted, "Senomyx will receive royalty payments based on sales of products containing new flavor ingredients developed under the agreement. This allows us to optimize the commercial potential of our cooling agents by collecting royalties on the sales of the flavor systems, rather than just the cooling compounds."

"Many [existing cooling] agents have deficiencies that restrict their utility, such as weak cooling characteristics, bitter off-taste, burning and tingling sensations, unwanted odor, limited solubility, and non-proprietary status," he added. "We believe that greater solubility, stability in high temperatures and a wide pH range could increase the number of applications for the cooling agents."

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"The Cool Flavor program is a little bit different from our others in that we decided that, because of the nature of cooling agents and how they're used in different product areas, it made sense to work with a single partner, Firmenich," says Zoller. "That's quite different from our other programs where the various programs are divided by the various receptor targets and applications and different product areas."

New Frontiers

While many of Senomyx's future endeavors are proprietary, Zoller did agree to discuss several innovations that may shape the company's future work. In 2007, Senomyx announced it had possibly discovered the primary protein receptor responsible for human salt taste: SNMX-29. "We've initiated, using this receptor, the identification of salt taste enhancers," says Zoller. "That was a very interesting series of studies. Through the analysis of all these different proteins that are in taste buds, we've identified some additional proteins that look like they could be taste receptors for something else. This is some of the exploratory work that we're doing that may be part of the programs of the future."

Reported by Jeb Gleason-Allured, Editor; jallured@allured.com