Innovations

Sniffing for success
Senomyx, Inc.

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As biology and business become ever more tightly entwined, the most basic of research is finding its way to venture capitalists. The latest beneficiaries are the olfactory and taste receptors being pursued by Senomyx, Inc. (La Jolla, California). Forget life-threatening disease and miraculous cures — these folks are going to bring you a world of delectable tastes and fragrant scents.

"We've put together big pharma's tools to come up with our discovery engine for smell and taste," says Senomyx CEO Paul Grayson. Grayson is targeting the consumer products industry because it spends billions on research, and yet so far has largely ignored the potential of genomics and molecular biology. Grayson's latest convert is his new vice-president of research, Mark Zoller. "I was looking around for something that was the next wave of using genomics," says Zoller, "and I think this is it."

Receptors and more receptors

> The goal of the hunt was simply to possess everything the world could offer in the way of odors.*

Senomyx was born in April 1999 thanks to the recent discovery of two putative taste receptors by Charles Zuker (University of California, San Diego) and Nicholas Ryba (National Institutes of Health, Bethesda, Maryland). Zuker teamed up with Lubert Stryer (Stanford University, Stanford, California) who he knew from, amongst other places, the scientific advisory board of Aurora Biosciences Corporation (San Diego, California). They recruited Grayson, then Aurora's senior vice-president of corporate development, as their first CEO. Stryer took off two years from Stanford to help found the company and act as its chief scientific officer.

From the initial idea of taste, the company quickly started thinking about the science of smell. The appeal was the lack of regulation ("Phase III clinical trials are basically someone smelling it," says Grayson) and the more developed state of the science.The molecular era of olfaction research had started in 1991 with the isolation of olfactory receptor genes by Linda Buck and Richard Axel (then both at Columbia University in New York). At last count there were ~1000 olfactory receptor genes in rats and mice and over 500 in humans (including pseudogenes).

> The precision of modern biological research comes to the rescue of the industry of smell.

Senomyx has intellectual property covering not only many of these olfactory receptors, but also a host of bitter taste receptors discovered by Zuker and Ryba earlier this year, and a method for expressing the receptors. Receptor expression failed initially because of a lack of membrane targeting; the solution was a fusion to the amino terminus of rhodopsin.

Decoding the matrix

> When Baldini assigned him a new scent ... Grenouille no longer reached for flacons and powders, but instead simply sat himself down at the table and wrote the formula straight out.

The first task for Senomyx is to come up with an olfactory code: a matrix in which every smelly chemical can be expressed as a pattern of activated olfactory receptors. "The proximal problem of what odors go with what receptor I think will be solved in the next two to four years," says Larry Katz (Duke University, Durham, North Carolina). "Relatively soon we'll have a molecular fingerprint of what an odorant looks like to the olfactory epithelium."

But will all those matrices make any sense? From Buck's work we know that each olfactory receptor recognizes multiple odorants (some clearly related, some not) and that each odorant is recognized by multiple receptors. Everyone involved is hoping that some sense of order falls out of this combinatorial code. Based on the psychophysics of smell and the psychobabble of perfumers "there are all these odor categories," says Katz, "and I think they must have correlations with groups of receptors."

Senomyx will use patterns for several activities, including screens for inhibitors of malodors. Perhaps the most lucrative application will be in establishing the code for a best-selling perfume, and then ensuring that the code is maintained even as the chemical mix is changed. Unnecessary components of complex perfume mixtures could be removed, expensive or unstable components replaced with cheaper, more stable chemicals, and new scent combinations devised to transmit the same odor signature from the far less volatile emulsion of a shampoo. In the land of Calvin Klein *et al.*, it's all about brand extension.

The receptor assays are a replacement human nose, capable of handling the thousands of novel chemicals that Senomyx is generating. "If you could screen 50,000 compounds a day with 1 μl of fragrance per assay in human subjects we would be out of business," says Grayson. "But you can't."

What Grayson cannot yet know is how exact his receptor patterns will have to be — and how exact of a match will have to be maintained — to preserve the precise scent of his choice. The work of Katz and Buck suggests that the number of receptors activated by any single odorant will be manageable. But establishing how sensitive the code is — to altered affinities or failure to bind 1 of 10 previously occupied receptors — will

*Italicized quotations are from "Perfume : the story of a murderer" © 1986 Patrick Süskind, published by Alfred A Knopf, Inc.

only come once the code is established and the system tested. Unfortunately, as Stryer says, “it’s easy to say in a sentence, but it’s a vast project to determine the olfactory response spectrum. It’s the most complex combinatorial recognition project.”

Will decoding reveal all, and does receptor biology equal olfaction? Complexity in olfaction does, indeed, arise largely from the multitude of receptors, and those receptors can be accessed by Senomyx using extracellular chemicals. The linkage from the receptors in the olfactory epithelium to the olfactory bulb is then simple — each olfactory sensory neuron appears to display only a single receptor, and all the dispersed neurons that display a given receptor converge on a single pair of glomeruli in the olfactory bulb.

Downstream of the glomeruli some extra complexity creeps in, including a temporal code identified by Gilles Laurent of the California Institute of Technology in Pasadena. Cells at this level “don’t work separately but interact and produce an emergent output,” says Laurent. “It’s very difficult to look at any of that in a reductionist way.” And the later complexities are necessary, says Laurent, “if you want to get something that is as reliable and as noise-resistant as the brain.”

For Senomyx, however, none of this may matter. “If you can mimic an activity pattern at the periphery you will get the same perception,” says Stryer. The brain take cares of the rest.

What no one is promising, at least so far, is mind control. “The emotional content, how odors bring back memories and make one feel, are very important, but receptors will not code all of that,” says Stryer. “I’m not in the position to say that a given receptor activation will seem pleasant.”

The science of the Snortal

Senomyx has competition, at least in the cloning of olfactory receptors, in the form of DigiScents, Inc. (Oakland, California). DigiScents was formed by Joel Bellenson and Dexster Smith after their success with the sequence-massaging company DoubleTwist, Inc. (Oakland, California; formerly Pangea Systems, Inc.). DigiScents promises that an odor-producing device called the iSmell “brings the sense of smell to your computer.” That’s right, folks, they are going to puff the smells of gunpowder, pine trees and burning tires at you as you surf the Net.

> The persuasive power of an odor cannot be fended off, it enters us like breath into our lungs, it fills us up, imbues us totally. There is no remedy for it.

Distribution of the necessary software will be easy — it is being bundled with RealPlayer — but the hardware (with its cartridge of 128 odorants, combinable in millions of permutations) presents more of a challenge. “The focus studies we’ve done have been very very successful,” says Bellenson. “The response rate has been over 90% once people experience it.” The trick may be to get people to try it in the first place — to get them past their memories of the classic John Waters’ film *Polyester*, a scratch-and-sniff extravaganza presented in “Odorama.”

The iSmell will be available by Christmas, but in the meantime DigiScents is busy cloning olfactory receptor genes (with the help of CLONTECH Laboratories, Inc. of Palo Alto, California) and determining an olfactory code akin to that being derived by Senomyx. “Those patterns become a fingerprint for an odor, which allows us to reproduce that odor later,” says Bellenson. “We pull the subjectivity out of the problem.” The code is the key to creating your very own “Scent Tracks™” by visiting a website called, you guessed it, The Snortal™.

A tasty alternative

For all its interest in olfaction, Senomyx may get its start in modifying taste. The simplest of all its proposed projects involves blocking the response of bitter taste receptors to products such as processed foods, nutraceuticals, antibiotics and artificial sweeteners. The number of bitter taste receptors appears to be manageable (perhaps 20–40), and any given bitter chemical may target only one receptor. “It’s more like a classical target,” says Zoller. In contrast, devising something new — say a tofu with meat flavor — involves creating new volatile and non-volatile components, and “that’s a really difficult problem.”

Projects for the future include novel sweeteners (based on proposed sweet receptors isolated by Zuker and Ryba), and modifiers of possible receptors for salt and umami (the flavor of monosodium glutamate). Senomyx is interested in doing further basic biology in these areas, including expression cloning of any receptors that may still be out there. “Since a lot of the work is done by homology and informatics, there is a lot that you can miss,” says Zoller.

The motivation

> The meaning and goal and purpose of his life had a higher destiny: nothing less than to revolutionize the odiferous world.

As a refugee from pharmaceutical science, Zoller has certainly thought about the contrast between his old and new goals. “When I tell non-scientists what I’m doing everybody thinks it is unbelievably cool,” he says. “When I tell scientists they think, ‘You’re not curing osteoporosis or cancer’.”

The new science “is very much targeted to enhancing the enjoyment of life,” says Stryer. “It relates to day-to-day living rather than the amelioration of suffering.” More serious applications may come, such as the modification of plant smells to repel insect predators. But with the current fuss over genetically modified foods “we’re not even going down that road,” says Grayson. “We’ll revolutionize one industry at a time.”

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