Dollars and scents: commercial opportunities in olfaction and taste

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Research successes over the past decade have provided a broad outline of the neuroscience of olfaction and taste. Our understanding of these systems now spans the molecular to the psychological. It will soon reach critical mass and begin to generate a variety of practical applications with commercial potential. Given the ubiquity of smell and taste and their importance to health, nutrition and quality of life, these applications could have a major impact on consumer product markets and create entirely new ones. Sensory biotechnology could be the first post-genomic application to break through to the consumer market. We describe odor modulation technologies with implications for food intake, health care and other arenas. Our deeper understanding of olfaction and taste in animal behavior and reproduction provides opportunities in pest control and animal husbandry, where environmentally neutral interventions are much in demand.

The chemical senses, taste and olfaction, are ripe with commercial promise. Yet despite recent advances in understanding their genetic and molecular mechanisms, they have not drawn the level of venture investment and commercial innovation we have come to expect in other fields. Genomics, biotechnology, and pharmaceuticals have all seen inventions made and companies started based on far more modest scientific work. Where are the olfactory and gustatory equivalents?

This lack of activity is especially puzzling given that fragrances and flavors are pervasive in daily life, and are used by consumers to make lifestyle choices in food, personal hygiene, household products and fashion. Modulating odor and taste perception may not be as imperative as finding a cure for Alzheimer's disease, but considering the size of the market and the potential impact on nutrition, health and well-being, it is certainly a useful application of neuroscience.

In addition to the lucrative and well-established consumer product markets, there are important opportunities in agriculture, animal husbandry and pest control. Smell may be a luxury in humans, but it is often the primary arbiter of behavior in animals ranging from nematode worms to mammals. This suggests a clear path to market for agricultural chemical ('ag-chem') products. Human applications, on the other hand, will require more innovative approaches. However, for those willing to seek out relevant consumer markets and build new product categories, much of the necessary basic science is at hand, and the potential rewards are great.

The genomics of smell and taste

Olfactory science came of age rather late. It wasn't until 1991 that mammalian olfactory receptor (OR) genes were discovered by Buck and Axel[1], putting an end to the debate on the fundamental nature of olfactory coding. Subsequent genomic research has shown us the broader horizon: a huge superfamily of some 1500 receptors mediating olfaction and taste, occupying almost 3% of the genome[2]. These are widely shared across mammalian species, although in humans no more than 350 olfactory receptor genes are functional[3,4]. Nonetheless, extensive homologies between mouse and human ORs indicate that the mouse may serve well as a model platform. The unexpectedly large number of receptors raises the question of how the olfactory system encodes sensory information. In contrast to vision, where three types of receptors underlie our perception of the entire visible spectrum, olfaction seems to use hundreds of receptors that each recognize multiple, but related, chemical compounds. In this way we are able to discriminate thousands of odors over wide concentrations[5].

In the gustatory system, five basic tastes—salty, sour, sweet, bitter and umami—are subserved by a combination of mechanisms. Salty and sour tastes are the result of specialized ion channels, whereas sweet and bitter appear to use G-protein-coupled receptors. Genes for the long-sought sweet and bitter receptors have been identified[6-8], and the notion of umami as a fifth basic taste was resoundingly endorsed with the recent discovery of two potential monosodium glutamate-specific receptors[9,10]. Our experience of the 'flavor' of food is in fact an amalgam of taste, olfaction and trigeminal sensation along with temperature and 'mouth feel'.

From lab to marketplace

In other fields, the discovery of a target receptor gene of wide functional importance triggers a land rush of academic research programs and piques the interest of venture capitalists. This has happened to a lesser extent in olfaction in part because of the sheer number of receptor–ligand relationships to be mapped. The first receptor–ligand pairing was documented only in 1998 using a laborious combination of adenovirus transfection and *in-vivo* electrophysiological recording[11]. High-throughput screening of odor ligands would be a more efficient solution to the mapping problem, but OR genes have proven exceptionally difficult to

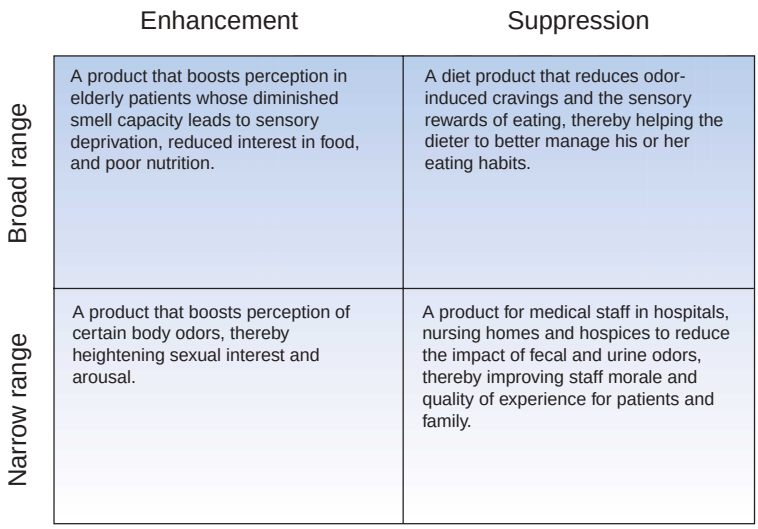

Fig. 1. Examples of possible odor modulation technologies. These can be classified based on whether they suppress or enhance the perception of an odor, as well as whether they act in a broad or narrow fashion.

express in heterologous systems. As a result, research and commercialization awaits a technical breakthrough. There has been slightly more success in expressing taste receptors for bitter and sweet, but only for a few of the nearly two dozen known receptors. Here too progress will be slow until a robust, high-throughput screening technology becomes available.

Still, given the importance of taste and smell in products from perfume to kitty litter and canned soup to ice cream, one would expect commercial interests to take the ball and run. Curiously, they have not. One reason lies in the economic landscape of the flavor and fragrance (F&F) business. Ten companies account for ~70% of worldwide F&F sales. Although they deal with smell and taste perception on a daily basis, these companies have traditionally preferred a supplier role and are reluctant to compete with their customers by marketing directly to consumers and/or by branding their technologies. By remaining providers of ingredients—which have lower profit margins than finished goods—F&F companies have less incentive to undertake the high costs and risks of commercializing developments in sensory neuroscience. This is in direct contrast to the pharmaceutical industry, but it does leave the field wide open for large consumer-product manufacturers with extensive R&D programs, as well as for tiny, nimble and highly focused startups.

Another barrier to commercialization lies in olfactory psychophysics, namely the tremendous amount of inter-individual variability in sensitivity, discrimination and hedonic evaluation. There is also variation at the ethnic and geographical levels[12]. Improved understanding of this variability would allow the empirical art of commercial fragrance development to become a predictive science for the first time. Evidence of a heritable component in odor perception[13,14] suggests that biological factors, including differences in receptor repertoire or expression, could have a role. The availability of biologically based markers for scent preference would be a marketer's dream. Odor-perception phenotypes[15] could be defined and mapped globally. These sensory-based consumer segmentations would provide a new way to match fragrances and flavors to consumers: a pharmacogenomics of olfaction.

Table 1. The US consumer market for scented products.

Toiletries (soaps, bath & body products, deodorants)	$6.6 billion
Hair care products	$6.1 billion
Laundry care products	$6.1 billion
Fragrances for men and women	$4.0 billion
Home fragrances	$2.3 billion

U.S. manufacturers' 2001 sales. Source: Kline & Company, Inc.

Consumer product applications

Chemosensory neuroscience can offer ways to more efficiently design and deliver pleasing scents and flavors. The major categories of scented consumer products (**Table 1**) are a substantial market, and technologies that improve product formulation or consumer perception will have a proportionately large economic impact.

Technologies to modulate odors are one specific area of promise. These would alter the response of the nose by molecular and physiological means, to block or enhance the perception of specific classes of smells. The products might be receptor agonists and antagonists, or compounds that interfere with other parts of the transduction process, or those that affect the control elements for gene expression. Odor-modulation technologies can be classified into those that suppress or enhance odor perception in either a broad or narrow range fashion (**Fig. 1**).

These potential applications encompass existing consumer product categories and point the way to new ones. Products that address consumer well-being are not necessarily pharmaceuticals, nor would they be marketed as drugs. However, as long as the pharmaceutical model dominates venture funding, sensory biotechnologies will trail the pack. Yet with some imaginative marketing, these hold the promise of becoming the next blockbuster consumer-sector innovations.

A few new entries into this area are pursuing the biotech model of venture financing and a discovery strategy. Senomyx Inc., based in California, has raised at least $59 million in funding since 1999. The company has obtained patent rights for the recently cloned sweet and bitter receptors and plans to license novel taste and smell molecules to major food and consumer product companies. Odor modulation technologies will be useful in food and beverage sectors, given that much of what we experience as flavor is due in fact to olfactory inputs. Linguagen Inc., a smaller company based in New Jersey, has a primary interest in bitter blockers that could be important in food and medicines. These companies are the vanguard of a new style of olfactory and taste ventures applying principles of modern biotechnology to consumer oriented markets.

Studies have found psychological and mood effects of perfumes as well as volatile steroidal compounds[16,17], and work on HLA-related human body odors demonstrates robust links among scent preferences, partner preference and fertility[18]. Such results suggest new ways into the marketplace. Once candidate materials are characterized by their empirical profile, commercial R&D can move ahead to claim substantiation. For example, California-based Pherin Pharmaceuticals, Inc. has clinical trials underway on compounds for PMS, social anxiety disorder and appetite stimulation.

It now appears that odor perception is impaired in a number of neurodegenerative disorders, including Alzheimer's disease, Parkinsonism and Huntington's disease. Upper respiratory tract infections and head injury take an additional toll on the sense of smell, especially among older people. Hence test methods and devices to quantify olfactory deficits may prove useful for diagnosis and for tracking disease progress and response to treatment. Several companies, including Cranial One Corp. and Burghardt GmbH, are newly active in this area.

Ag-chem applications

Odors from the environment and conspecifics strongly determine behavior for many insects and small mammals. Together, these species destroy more than an estimated 30% of the world's annual food production, some of it in the field and a significant portion of it in the value-added, post-harvest stage of processed products. Storage and distribution of food are of equal importance to field production in combating hunger. Insects are also vectors for a litany of afflictions that includes malaria, Lyme disease and the newly worrisome West Nile virus. Caught between deleterious environmental effects and the emergence of resistant strains, the use of pesticides is approaching its limits. In contrast, the integrated pest management approach seeks naturally occurring and environmentally benign olfactory compounds for use as repellents, attractants (for trapping) and antagonists (masking compounds). These efforts are encouraged by the size of the ag-chem market for insect control (estimated at more than ~$8 billion annually) and the market for personal insect repellents (estimated at over $2 billion). The availability of environmentally sound and personally safe products might be expected to increase those markets significantly.

A molecular underpinning for these products is the identification of odor receptor genes in the fruit fly *Drosophila* and in *Anopheles*, the mosquito that carries malaria[19,20]. Here, too, an obstacle has been the heterologous expression of receptors in a high-throughput screening system, but the generally smaller receptor families (~100) makes this less of a problem. There are several development-stage companies working in this area, and rapid progress might be expected. Among them are Sentigen, Chemasense and Inscent. Each of these biotech-oriented companies are focusing on different aspects of insect control through olfactory compounds.

Animal-oriented products are not limited to insects but may include food animals, in which many husbandry concerns, from feeding to mating, could benefit from olfactory cues. Rodent and other non-insect pest control, an issue of great importance to municipalities and food storage facilities, could also be targets of olfactory and gustatory compounds that would have far less toxicity than currently available poisons. This is also an effort ideally suited to public–private partnerships.

Biological olfactory systems are among the best chemical detectors on the planet, especially as regards discrimination and the diversity of detectable compounds, raising the intriguing possibility of animal-based applications. For example, a recent news report told of bees undergoing successful one-trial training to detect the odor of explosives, and their approach and avoidance behavior could form the basis of a system of land mine detection (Sandia National Labs, 2001 Annual Report). Using insects rather than dogs for such work has advantages—less time spent in training and smaller economic and emotional consequences should a tracker animal be lost.

Future outlook

When might we see products based on the science of olfaction and taste? In some areas—such as pest control and animal husbandry—first-generation products are within the reach of current knowledge. Other areas—such as consumer applications—await recognition by the investment community that 'biotech' has a broader reach than pharmaceuticals and medical devices. With its less-crowded competitive landscape, lower regulatory hurdles, and faster time to market, sensory biotechnology should look attractive to the investment community. Imaginative venture capitalists wanted.

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