Commercial Perfumery and the Molecular Genetics of Olfaction

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In 1991, Columbia University researchers Linda Buck and Richard Axel stunned the scientific world by announcing the discovery of the genes that create the odor receptor proteins in our nose.[1] The repercussions of that major discovery continue to be felt today. The most immediate effect is on olfactory research: it changes how scientists conceive of the physical mechanism of odor detection. Next, the discovery changes our view of higher levels of information processing in the brain. Finally, Buck and Axel's finding promises to change forever the way the fragrance industry approaches the art and science of perfumery.

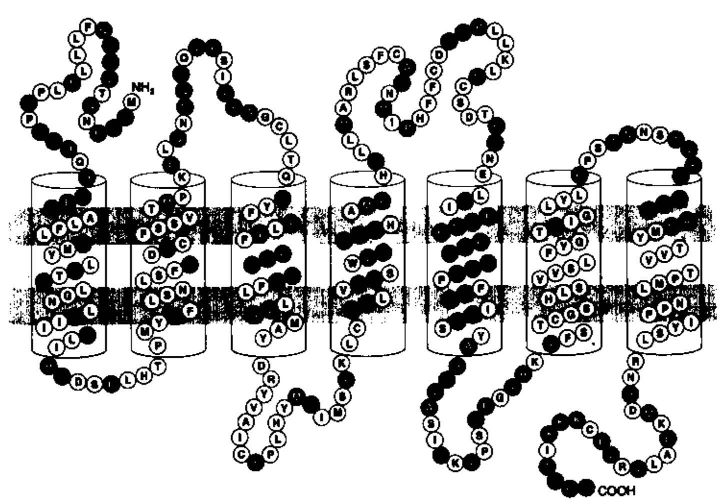

Figure 1. A diagram of one of the putative receptor proteins (cDNA clone I15) discovered by Linda Buck and Richard Axel. The cylinders represent α helices spanning the membrane of the receptor cell; the N-terminus of the protein is located extracellularly, the C-terminus intracellularly. Each ball represents an amino acid; positions shown in white share the same residue in 60% or more of sequences, and the more variable residues are shown in black.

The Nasal Genotype: A Diversity of Odor Receptor Molecules

The most dramatic aspect of Buck and Axel's work was that it solved a very old scientific problem concerning the physical nature of odor detection. The primary sensory neurons in the nose are thought to make contact with odor molecules by means of protein receptor structures located in the cell membrane. Activation of these putative receptors by odor molecules of an appropriate size, shape and charge leads to the opening of ion channels in the cell membrane, and ultimately, to the production of a nerve impulse. The question that has long challenged researchers is: does the olfactory system use a few receptor types to recognize many odor molecules, or does it make use of many receptor types? The definitive answer: there is a large and diverse multigene family of receptor proteins. There may be as many as 1000 different receptors in action in the human nose.

The newly discovered receptor proteins appear to belong to the superfamily of seven transmembrane domain proteins. Proteins of this type, so named because each one is stitched seven times through the cell membrane, are known to serve as receptors for hormones and neurotransmitters (Figure 1). Previously known seven transmembrane domain proteins detect specific molecules circulating in the bloodstream, and thereby assist the body's internal communication. The newly discovered, but structurally similar, odor receptor proteins detect volatile molecules

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present outside the body, and make possible the body's chemical communication with the external environment.

The pioneering work by Buck and Axel will now set off an avalanche of gene sequence data. Dozens of laboratories across the globe can read the DNA code and spell out the protein sequences of the odor receptors. In time, we will be able to exhaustively specify the receptor proteins expressed by any person reading this article. The collection of molecular receptor shapes that are present in your nose constitutes your nasal genotype. By the end of this decade, you will be able to know your nasal genotype just as easily as you know your blood type.

The next step for molecular biologists is to determine which of the 1000 receptors are truly functionally different. Based on the sequences identified by Buck and Axel in the mouse, there appear to be about ten subfamilies composed of closely similar nucleotide sequences. Some minor variations in the genetic code may not appreciably alter how effectively or selectively the receptor binds odor molecules. By ignoring the nonfunctional genes, it will be possible to reduce the avalanche of diversity to a few mere heaps (Figure 2).

There will be an important difference between knowing your blood type and knowing your nasal genotype. Red blood cells bind oxygen equally well regardless of blood type. But your nasal genotype may determine what you are able to smell, how sensitive you are to it, and even the resulting perception of odor quality.

The Commercial Environment and the Physical Environment

Genotypes evolve through the process of Darwinian natural selection. This process takes place in a specific physical world that limits and shapes the course of evolution. What is the selective environment of the nasal genotype?

Here too we find incredible diversity. Store shelves and counters are filled with an array of scents, from the rich floral and fruity accords of *Poison*, to the fresh green notes of *Chanel 19*, to the warm, sensual woody blends of *Obsession* and the other oriental scents. The American psychologist William James once spoke of the "blooming buzzing confusion of the sensory world." We should amend this to the blooming, buzzing, volatilizing confusion of the multisensory world.

The sensory diversification of the fragrance market has been driven by a single overriding goal: to entice the consumer by olfactory means in order to increase sales of product. On closer inspection, the perfumer's design task is in a way analogous to two classic phenomena of evolutionary biology: pollination and seed dispersal.

A non-self-fertilizing plant must attract animals in order to carry pollen to other members of its species. Following fertilization and the production of mature seeds, the plant needs to attract animals that disperse its seeds to new areas. A plant often accomplishes these goals of attraction by means of a sensory appeal to an animal's nose. The smells of flowers and fruits are designed by the process of evolution as inducements and biological advertisements. They attract pollinators to flowers and nectar sources, and seed dispersers to fruits and edible seed pods.

Roman Kaiser, a researcher at Givaudan-Roure's laboratories in Dübendorf, Switzerland, is a fragrance chemist who is also an expert on orchids and other flowering plants. He has made a thorough chemical analysis of the fragrance emitted by hundreds of orchids, and has related these scents to the ecological circumstances of each species, including the type of pollinator the fragrance attracts. His work, conducted over the course of 20 years, provides a superb illustration of fragrance as an evolved biological advertisement, and indeed illuminates the nature of the engine driving the evolution of fragrance diversity in the physical world.[2,3]

By analogy to the biological world, scented brands are the species in the Darwinian marketplace, and it is critical that they attract consumers. Sales correspond to biological reproduction: in each case, more copies are produced as a consequence. Stretching this analogy to the limit, market share corresponds to ecological dominance (we already speak of niche brands), and the appearance of a new line extension is a mutation event. In the Darwinian marketplace, as in the biological world, the goal of the olfactory advertisement is the same: attraction on the basis of a sensory appeal.

Buck and Axel's discovery of genes for the olfactory receptors will soon allow us to identify the nasal genotype of the consuming public. Is it possible that this new knowledge will replace traditional demographics as the best descriptor of the market?

The Missing Link: Individual Fragrance Phenotypes

The difficulty with a strictly gene-based view of the future fragrance market is that products are not marketed to blue eyes or olive skins. A scent must appeal to an entire individual, who happens to have particular genetic traits such as blue eyes or olive skin. In the same way, we cannot design fragrance for olfactory receptor protein number FX-347, without taking into account how that receptor operates in the context of a perceiving individual.

In other words, knowing a consumer's nasal genotype is not the whole story. By itself, the nasal genotype will not help us optimize fragrance design and sell more product. Though it can be precisely spelled out by high tech molecular biology, the nasal genotype is merely a grab-bag of particulate traits.

What we need to know is how these traits add up and are expressed in a whole, perceiving individual; this is what biologists call a phenotype, and what marketers call a consumer.

Our challenge is to describe the psychological reality of what I call the fragrance phenotype. It is the fragrance phenotype that will link the newly discovered olfactory genes to the sensory-based behavior of our consumers.

Our fragrance phenotype is the totality of olfactory sensations and perceptions that we, as individuals, are able to experience. The olfactory phenotype can be described and quantified by psychophysical techniques, that is, by

precise sensory measurements. There is great inter-individual variation in the fragrance phenotype. The specific anosmias provide a good illustration. To take one case, some people are extraordinarily sensitive to the odor of androstenone, and are able to detect it at exceedingly low concentrations. Others are unable to detect androstenone even at massive concentrations, yet they display the normal range of sensitivity to other odorants. Such people are said to have a specific anosmia for androstenone.

The perception of certain musk notes provides another example of inter-individual variation in the fragrance phenotype. To some people, Galaxolide has a musky odor quality while to others it is more woody, and yet to others it is primarily floral. Thus, not only sensitivity, but the perception of odor quality constitutes the fragrance phenotype.

By linking analysis of the fragrance phenotype to the nasal genotype, we may discover far more subtle and surprising variation in odor perception. There may, for example, be a consistent difference in the perception of jasmine that becomes evident only after the smellers have been sorted by their nasal genotype. We will be able to combine this approach with pedigree analysis to uncover new bases of consumer behavior. Perhaps consistent brand (and therefore scent) use by members of a family is traceable to their shared odor receptor genes. We may, in addition, be able to elucidate a role for nasal genotype and fragrance phenotype in racial differences in scent preference.

Underlying the measurable responses that form the fragrance phenotype are psychological structures that filter the input from receptor molecules, and olfactory neurons and transform it into an interpretable whole. The fragrance phenotype is what made survival and Darwinian success possible for our prehistoric ancestors. It is what makes aesthetic judgments and preferences possible for us today. It is the critical parameter in fragrance design for the future.

Evolving for the Future: Optimizing Perfumery via Nasal Genotype and Fragrance Phenotype

Perhaps within five years, it will be possible to assemble gene sequences that code for evolutionarily novel odor receptors. Inserted into our own DNA, these artificial genes may produce entirely new odor sensations—fragrances yet undreamed of.

Technological advance has always redefined chic. Consider this cyberpunk vision: by the mid-21st century, elective gene alteration for augmented odor perception could become an aesthetic trend. Orchid fanciers will be able to enhance their personal olfactory appreciation of their collections.

Persons with augmented sensitivity to human pheromones will add a new dimension to social behavior in clubs and discos. Neuro-delinquents will use gene-altered tolerance for body malodors to further the social distance between themselves and what is left of mainstream society.

After the tidal wave of molecular genetics, the art and commerce of perfumery will never be the same. Today's fragrances are crafted by perfumers trained in the aesthetic traditions of the Renaissance. These artisans, who spend years in apprenticeship, talk quaintly of amber notes and white floral accords. By the year 2000, perfumers will speak routinely of musk-receptor agonists, and the molecular binding affinities of floral-receptor proteins.

The practice of perfumery will be inconceivable without software for computer-aided design and molecular modeling. The perfumer's assistant, loyally pouring together ingredients for the master's latest creation, will be as anachronistic as the eye-shaded clerk in a Victorian counting house.

Computers will translate a gene sequence into a 3-D model of the receptor, and screen thousands of odor molecules to find the few that optimally activate it. Ask for more of a lavender nuance in your new hand soap, and the microprocessor will recommend a stereoisomer with a higher binding affinity for receptor protein FX-347.

Some receptors specialize in the acrid notes of ripe laundry, others in the stench of a dirty diaper. The perfumer of the future will design a molecule to fill the receptor site without activating it, producing the ultimate malodor blocker. An inhaler full of designer molecules will replace the plumber's traditional cigar.

The mental processing of olfactory sensation is at once precise and allusive. With psychology as sophisticated as today's biotech, we will achieve a complete reckoning of the language of fragrance, the sensory vocabulary that J.-K. Huysmans called "subtle as any human tongue, yet wonderfully concise under its apparent vagueness and ambiguity."

Should today's perfumer or fragrance chemist fear this future? More importantly, will there be a place for the artistic creativity that has, for centuries, been the hallmark of perfumery? I believe there will be. In fact, it is likely that after a period of bewilderment and resistance, the most creative persons in the fragrance industry will find the biotech approach to be liberating. The advent of gas chromatography and mass spectroscopy were met initially with anxiety and mistrust, and yet these techniques have become a daily part of life, and have, in the end enriched, not belittled, the perfumer's heritage. As we progress in our understanding of the fragrance phenotype, we are certain to open even more doors for creative endeavour.

References

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