From molecules to perception: 126 years at the forefront of olfactory science

Firmenich
for good, naturally

Olfaction is one of the most elusive of the human senses. It sustains life by enabling several critical functions, such as our ability to locate and select food, our choice of mates, influencing our social life and helping with danger avoidance. And the olfactory system has the striking ability to elicit powerful emotions, feelings, and memories, thereby impacting quality of life. These qualities, and our resulting, inherent attraction to fragrance, have driven firms like Firmenich, the world's largest privately owned perfume and taste company, to explore the mysteries of olfaction and to be innovatory in developing fragrance and flavour.

Despite olfaction's vital role, our understanding of its mechanisms is still limited. Complex biochemistry is at play in our olfactive response as soon as we develop in the womb. Odorants, mostly organic molecules that are released into the womb or in our atmospheric environment after birth, are detected by specialized olfactory receptor cells in the nasal cavity. The odorants are then transformed into spatiotemporal patterns of neural activity in the olfactory bulb and central nervous system, and decoded by the brain to generate a perceptual 'odour object' that enables us to recognize the identity, intensity, and valence of an odour. Odorants induce a variety of responses, from giving simple behavioural signals to generating sophisticated cognitive and emotional changes or feelings.

Human responses to smell are at the root of the demand for fragrances and the growth of a global industry. Scents elicit human emotions such as happiness, relaxation and excitement, and evoke profound memories. The delights of perfume were known to ancient civilizations; references to perfume and incense bringing joy to the heart are found in the Bible. By the late nineteenth century, perfumery was booming, gripped by transformation from an artisanal activity to industrial-scale production for the modern consumer era. Organic chemistry had opened new avenues to produce rare and expensive natural ingredients that usually were distilled or pressed from raw plants. Science would continue to shape the development of fragrance and flavours over the next century, driving the need for deeper understanding and opening up opportunities for innovation.

Figure 1. Leopold Ružička elucidated the structure of two musk odour molecules while he was head of Firmenech's research laboratory, paving the way for the production of musks for perfumery.

PIONEERING THE TECHNOLOGY OF SCENT

On November 1, 1895, a daring Swiss chemist and a young businessman set up their laboratory in a rented garage in Geneva, Switzerland, seeking to ride the wave of this technological boom. Philippe Chuit and Martin Naef would not become global household names like the Silicon Valley entrepreneurs who followed a similar template nearly a century later. But they were driven by a similar spirit of innovation, and soon became renowned in their trade. Chuit had developed a new process to synthesize vanillin, at the time a recently discovered ingredient prized by perfumers.

Over the following century, molecules and pioneering olfactory science would become the building blocks of a global business-to-business perfume and taste company. Today, Firmenich employs 10,000 people, comprises six research centers in Geneva, Switzerland; Princeton and San Diego in the United States; Beijing; Gujarat in India; and Castets in France, manages a portfolio of more than 4,000 active patents and, in 2021, generated an annual turnover of CHF 4.3 billion.

The group serves the body and home care, fine fragrance, food and beverage industries, extending to support for health and wellness. Firmenich ingredients are found in everyday products used by consumers worldwide.

From an early focus on synthesizing prized fragrance ingredients, and in the mid-twentieth century to supply and develop flavour ingredients, the scope of scientific endeavour at Firmenich and its sophistication have grown exponentially. The science now extends well beyond chemistry. Scientific understanding of the discovery and development of ingredients and of the mechanisms of human olfaction has also evolved significantly. While science continues to enable us to harness the best of nature with efficient natural extraction technologies, it has also expanded our capacity to reduce impacts on scarce natural resources from the outset of research, including the application of green chemistry principles and biotechnology for ingredient production.

The human senses, primarily taste and smell, but also sight and touch, are at the heart of our development of new fragrances and flavours. Today, Firmenich is engaged in research on the pathways of odour and taste perception, from the physiochemistry of emission of a fragrance or flavour at its source to the detection of these substances in our tongue and nose, and ultimately their perception in our brain – all to understand which sensory characteristics drive consumer preferences and positive emotions. The company's in-house research and development team is multidisciplinary, encompassing biotechnology, analytical and organic chemistry, biochemistry, microbiology, receptor biology, plant biology, psychophysics, materials science, data science and process engineering.

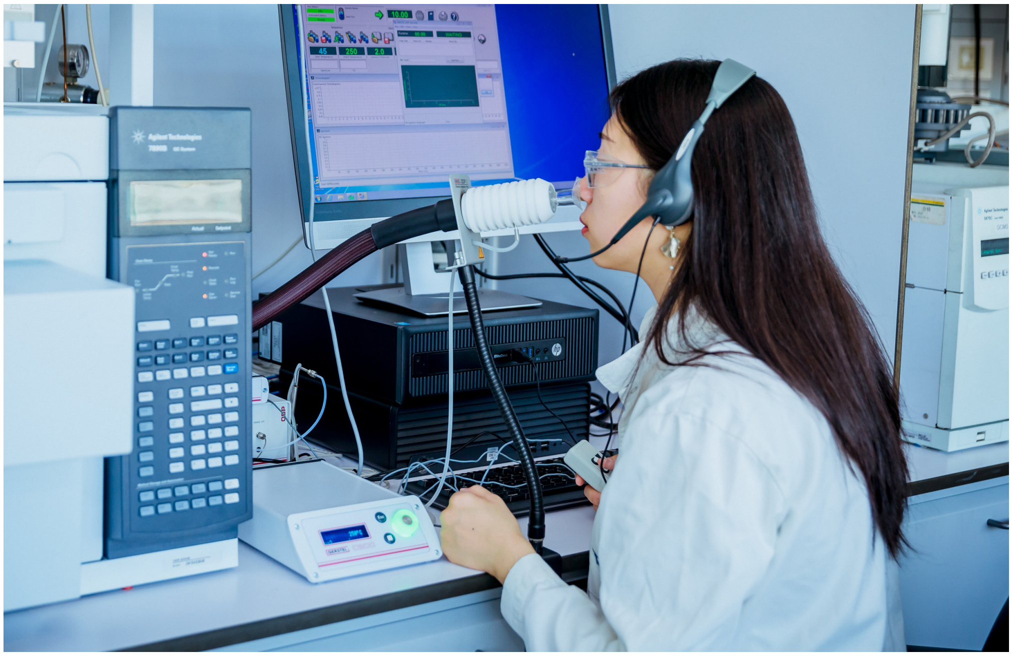

Figure 2. A researcher uses an instrument called a gas chromatograph (GC). The process of gas chromatography-olfactometry (GC-O) uses a GC to separate the volatile compounds, and then the odour is detected using an olfactometer.

DISCOVERING FRAGRANCE MOLECULES

Within three years, Chuit and Naef had moved from the garage at the end of Charles Firmenich's garden into new industrial premises in Geneva and employed more than 20 people. The ties with the Firmenich family deepened through marriage and business. By 1900, Frédéric Firmenich, an entrepreneur, had joined the duo. The company would eventually be renamed Firmenich & Cie in 1934, after Chuit and Naef's retirement, and remains family owned to this day.

Together, Chuit, Naef and Frédéric Firmenich developed the model that has shaped the success of Firmenich. Science and innovation were the engines of growth, combining with creativity, commercial acumen and long-term vision to produce desirable and high-quality fragrance – and later taste – ingredients for producers of consumer goods.

Chuit was more than an inventive and skilled scientist. He also gained a reputation as a 'nez' ('nose'), a perfumer with a fine sense of smell. Initially specializing in floral notes, he was capable of identifying and developing molecules, combining them to make appealing fragrances and developing production at sufficient scale to sell them to business customers. He also set out to push the boundaries of human olfaction, inventing smells that appeared to be new, not simply to imitate nature.

An early tribute to his innovation came in 1904. Chuit had conjured up violettone and Dianthine, a spicy combination of carnation, rose and iris, which attracted French perfumer François Coty, a revolutionary figure in modern perfumery. A decade later, when French fashion houses joined the perfumery business as well, the company recruited perfumer Maurice Chevron in Paris. Since then, Firmenich's science-led research team has worked closely with talented in-house perfumers who have carved out award-winning reputations in their own right in the creative world of fragrance.

Chuit was constantly seeking to boost the company's capacity for innovation. By 1921, he had developed a research programme that drew on cooperation with academic institutions, effectively forming the equivalent of a modern-day incubator. Leopold Ružička of ETH, the Swiss Federal Institute of Technology in Zurich, was among those who were offered laboratory space in Geneva, and the prospect of a relative degree of independence (**Fig. 1**). Ružička brought experience from a team at the forefront of research into terpenes and macrocyclic compounds.

It was a meeting of minds and the personal chemistry was reflected in their leading-edge science. While Chuit focused more on industrial research, Ružička became head of the research laboratory from 1925 to 1927. He set the direction for olfactory discovery and subsequently maintained an influential role in Firmenich science for the rest of his career as a professor. A first avenue was musk odour, a prized ingredient in perfumery because of its capacity to heighten olfactory perception, which was largely procured from

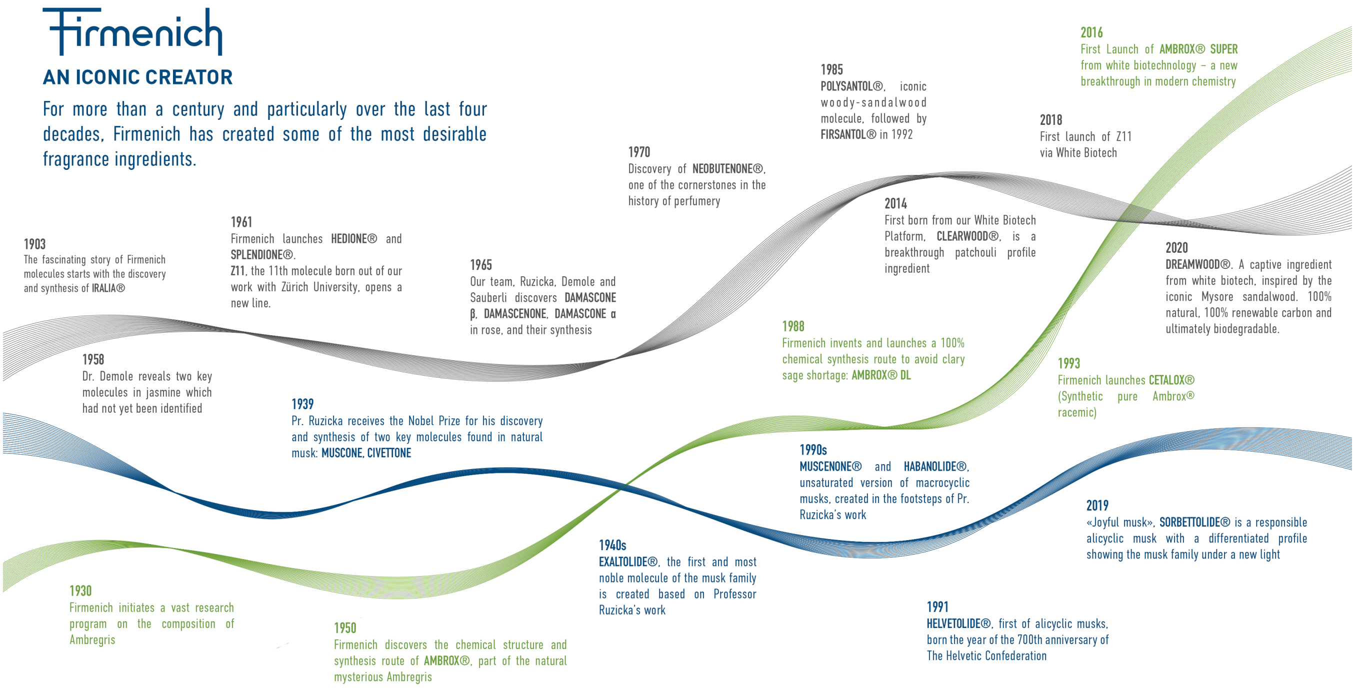

Figure 3. Defining ingredients. Molecular and receptor science has enabled Firmenich to create ingredients that shape modern fragrance.

deer or civet cats at the time. Ružička's work on substitutes for naturally occurring musk odour allowed him to elucidate the structure of two key molecules, muscone and civetone. In 1925, Firmenich started production of Exaltone, an initial ingredient to emerge from this body of research.

Ružička was jointly awarded the Nobel prize in chemistry in 1939, with Adolf Friedrich Johann Butenandt, for his work on polymethylenes and higher terpenes, and his research for fragrances was acknowledged in the Nobel citation. This era marked the beginning of close collaboration with academic researchers that is replicated today in Firmenich's network of open innovation partners worldwide, ranging from renowned research institutes and academics to dynamic start-ups (**Fig. 2**).

UNRAVELLING THE SENSE OF SMELL

These relationships were pivotal for smell and taste research. To mark the company's seventy-fifth anniversary in 1970, the then chief executive officer, Roger Firmenich, an accomplished chemist, organized an international symposium on gustation and olfaction. Ružička was celebrated at the event by fellow scientists. But the symposium also had its sights on new frontiers, signalling growing interest in the nascent field of chemoreception and research on the senses of smell and taste.

Ružička, his former laboratory assistant and successor Max Stoll, and subsequent Firmenich research heads Edouard Demole and Gunther Ohloff, were among a long line of scientists in a variety of commercial or academic settings who made significant progress during the twentieth century in deciphering the chemical identity of odorants (**Fig. 3**). They helped shape the fragrance industry by leading discoveries such as Hedione, an emblematic ingredient capturing the freshness of jasmine, Ambrox, a substitute for ambergris, and rose ketone bases. By 2014, Firmenich launched the first in a succession of renewable perfumery ingredients obtained from biomass using industrial biotechnology, including Clearwood, reminiscent of rare patchouli oil, and most recently Dreamwood in 2020, inspired by Mysore sandalwood, a protected plant species.

In more recent decades, science has gradually been decoding the mysteries of our perception of smells. Researchers have made inroads in characterizing the human brain's responses to odorants and in elucidating the molecular and genetic components involved in reception and transduction – the conversion of smells into electrical signals.

In particular, in vertebrates, the ability to perceive a wide variety of organic molecules, and to distinguish between them, is made possible by the existence of a huge family of odorant receptors. These receptors also enable the encoding of the odour in a combinatorial manner. Linda Buck and Richard Axel, the 2004 Nobel laureates for medicine and physiology, heralded a new era of smell research in the twenty-first century with their discoveries on odorant receptors and the organization of the olfactory system, identifying approximately 1,000 receptor genes in rodents. From thinking focused on one receptor per odour, this breakthrough sparked research into the mechanisms by which the odorant receptors can decode the complexity of odours, their types or combinations and the differentiated way receptors may detect them.

Receptor biology has shed new light on the mechanisms behind odour perception, but there is still a lot to uncover. Cognitive sciences also unlock further understanding of the human senses by helping to map how smell and taste stimuli are transformed into physiological, cognitive and emotional responses. Research into the highly complex interactions of molecules with hundreds of olfactory receptors in the human nose has given us an edge in understanding the mechanisms of olfaction. But many more avenues are ripe for discovery.

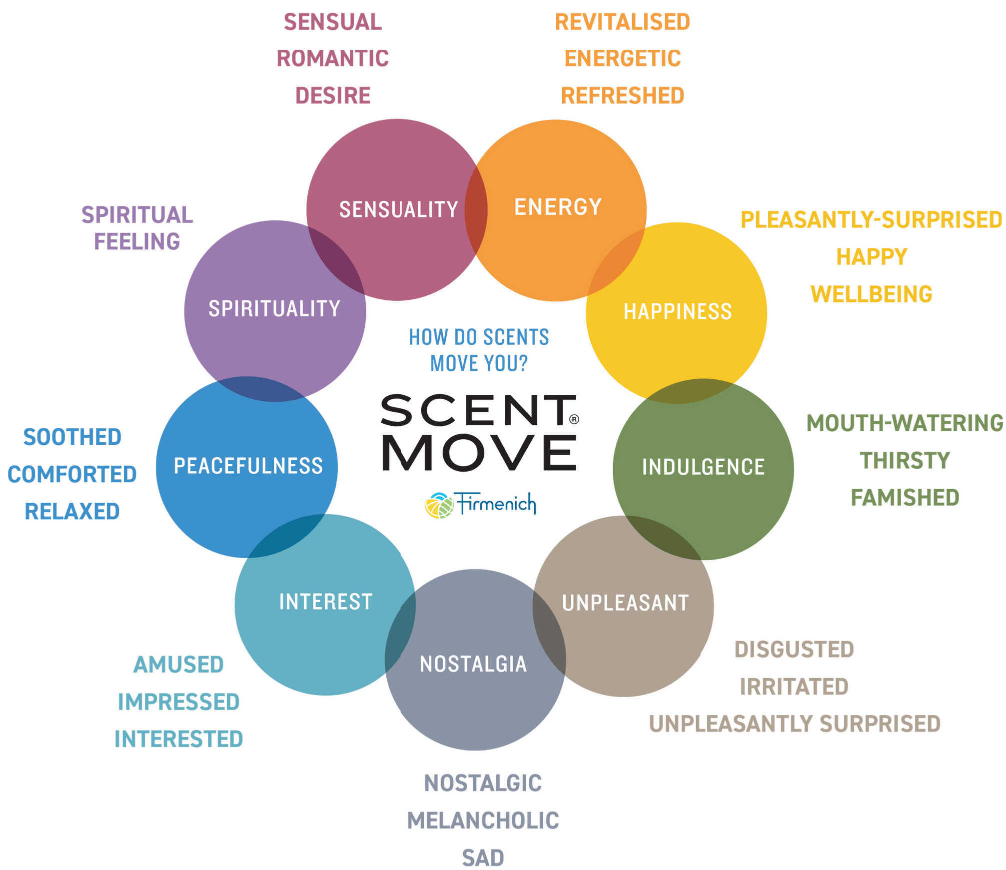

Figure 4. Evaluating feelings. Derived from research on cognitive responses, Firmenich's unique ScentMove tool provides a template for verbalization of emotions and enables the evaluation of feelings elicited by odours and fragrances.

EXPLORING FRESH INSIGHTS ON OLFACTION

More recent observation that most odorants may act as an agonist or antagonist of a specific receptor demonstrates the possibility of generating an almost infinite number of possible codes, potentially translating into an almost infinite number of odours[1,2]. The discovery of these antagonists has enabled new and highly effective approaches to malodour control. By naturally blocking the activity of the malodour receptor, antagonists of faecal malodour receptors temporarily and reversibly reduce the perceived intensity of the bad smell. The expansion of the combinatorial model to antagonism has spurred new research into identification of the most effective combinations of antagonists and how to deliver them at effective levels for each type of product.

Currently, there are gaps in the understanding of the molecular interactions of odorants with the apparently promiscuous olfactory receptors of terrestrial organisms. The existence of agonism, competitive antagonism, and allosteric modulation might explain the difficulty in predicting the smell of a mixture based on its components, as well as the fragrance industry's need for the accumulated craft of perfumers and their acute sense of smell, acquired over many years of training and experience. Data science and artificial intelligence provide powerful tools to explore new solutions.

The complex interactions between an odour and its receptor(s) should provide a new lens to probe fundamental questions about how odour is encoded in the periphery. They shed new light on the long-standing paradox that odours with widely different chemical structures can generate the same odour percept. This might be related to the phenomenon of concentration invariance – the perceived odour quality remains the same over a wide range of concentrations for many odorants, despite the recruitment of additional olfactory receptors with increasing amounts of odorant. The timing of electrical signalling in the olfactory bulb has very recently been shown to establish a hierarchy among odorant receptors, with shorter latencies for high affinity receptors, granting them a major role in shaping the output olfactory message to the brain[3]. Furthermore, the huge interindividual variability of the genetic makeup of the odorant receptors has been shown to determine sensitivity and odour perception[4]. This makes it even more difficult to elucidate how the vertebrate brain interprets the molecular receptor code in the periphery.

Psycho-physiology, examining issues such as heart rate or skin conductivity with smell or taste, is one of the most recent tools to be added to the olfactory researcher's box. Researchers are gaining fresh understanding of transduction, the conversion of sensation into electrical signals to the brain, but little account for odour perception. This is why advanced, dynamic and high-resolution brain imaging is needed to correlate these avenues of research and better understand our physiological response to scent.

These new methods are also key to the study of the fate and significance of the olfactory message in humans. As in all vertebrates, the human olfactory system has very direct connections to the emotion and navigation centers in the brain.

Behavioural observations across animal species have provided insight into a rich collection of transformations and behaviours that are elicited by olfaction and dependent on context. In mammals, the olfactory system is also intensely connected to respiration and mouth activity[5]. As a result, odorants inhaled through a sniff of surrounding air may elicit a different sensation than the same odorants detected during expiration of air expelled when food is chewed[6]. Furthermore, effects as diverse as pheromonal communication, recognition of relatives, fear transmission, food tracking and homing, have been documented. Scientists today wonder to what extent may some of these effects subsist in humans.

The ancient view that humans have a poor sense of smell relative to other species is no longer pertinent[7]. Rigorous scientific

Firmenich is researching how smells can affect someone's emotions and mental state.

research has demonstrated the possibility of pheromonal cues in the interaction of mothers and newborn children[8] or in fear transmission[9].

More frequently, research has focused on the indirect effects of fragrances, which rely on associations and memories to resuscitate the affective context of a past experience of a given smell. The French novelist Marcel Proust captured the concept perfectly with his description of the madeleine, a small sponge cake that evoked pleasant smells or tastes reminding his fictional character of childhood.

Through long-term collaboration with an academic research partner, Firmenich has jointly studied the affective responses of humans to perfumes and aromas (**Fig. 4**). These culture-specific responses may consistently be mapped over several dimensions[10]. Remarkably, the major affective dimensions elicited by a collection of perfumes were found to correlate with functional magnetic resonance imaging (fMRI) brain response patterns[11].

NEW APPLICATIONS FOR WELLBEING

The scientific investigation of our oldest sense is continuing to yield many surprises, whether to do with well-being, the development of newborn children, or how individuals interact in society. Despite the pace of discovery in the past two decades, the recent observations of anosmia in some people who have contracted COVID-19, and questions surrounding its broader impact on their mental and physical health, have highlighted how much we still have to discover about the human biology of smell and taste. This has sparked a new wave of research into the role of the olfactory system, odorant receptors, and even the nasal microbiome as possible diagnostic indicators or therapeutic targets for the onset of human diseases[12].

Firmenich's purpose goes beyond delighting the senses. Exploration of these frontiers of science allows us to generate sweet or savoury tastes without sugar or with less salt, to enhance sensations such as coolness, or modulate bitterness; and discover how to improve fragrance formulations by counteracting odour adaptation/habituation, or provide targeted malodour control. In recent years, this research has yielded innovative and sustainable applications that enhance wellbeing, including by supporting sanitation, sugar or salt reduction. Through our research centres, we are investigating how odour impacts our emotional and mental health. This global network also allows us to examine why and how the same tastes and smells may evoke different responses in different contexts and cultures so that we can design solutions tailored for specific markets.

A credible legacy of scientific innovation and collaboration, as well as a track record of responsible business, has guided Firmenich's path for more than 125 years. Rigorous and collaborative multidisciplinary research on olfaction, extending from molecules to perception, is paving the way for new generations of safe and renewable ingredients that benefit consumers and can enhance wellbeing.

Our research aims to connect the dots between the signal induced by a fragrance molecule, the activation of a receptor, and individual physiological and emotional responses. By understanding each step in the process and their interlinkages, as scientists we are striving for greater understanding of the human body and the human experience.

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