Chemorception is the aptitude of living organisms to identify natural or synthetic chemical compounds in their environment and to evaluate their concentration.[1-4] In April 1970, the organic chemist Robert Luft was asked how volatile odorant molecules are perceived by the olfactory system. “Si vous répondez à cette question,” he replied, “le Prix Nobel est à vous.”[5] The 2004 Nobel Prize in Medicine was awarded 34 years later to Richard Axel and Linda B. Buck of the Howard Hughes Medical Institute, who deciphered the molecular basis for the perception of odors and the corresponding information preprocessing in the olfactory system. From the viewpoint of a chemist, these studies offer fascinating perspectives.

Olfaction is initiated by a molecular interaction of chemical compounds called odorants with the olfactory neurons located in the epithelium of the nasal cavity. The required molecular properties of odorants were determined to be a moderate molecular weight, low polarity, a certain water solubility, high vapor pressure, and lipophilicity.[1] The existence of peripheral olfactory receptor (OR) proteins located in the cilia of sensory neurons in the epithelium had been postulated but remained unproven prior to the work of Axel and Buck.[4] Numerous theories had been formulated concerning the mode of interaction between odorant molecules and the olfactory neurons, including the vibrational theory,[5,6] the membrane-diffusion theory,[7] the Piezzo effect,[8] complexation,[9] the polarization theory,[10] the chromatography analogy,[11] the hydrogen-bond-dispersion model,[12] and the tunneling vibrational theory.[13,14]

Since 1949, it had been thought that only the characteristic molecular shape of an odorant determined its odor.[15,16] Based on the identification of a number of different types of anosmia (the lack of a sense of smell), it was concluded that as many (between 7 and 30) specific receptors with the capacity to recognize different molecular shapes must exist. Thus, the existence of an “alphabet” of odor types with corresponding molecular shapes was postulated. The combination of the letters of this alphabet should lead to the perception of a multitude of different odors.[17] Since then, numerous chemical studies have been devoted to the elucidation of structure–odor relationships.[18,19] Despite some success with specific series of molecules and their odors (e.g. musks, ambergris, sandalwood), numerous discrepancies and exceptions remained.[20] Furthermore, it remained impossible to predict the odor of a molecule from its molecular structure. These difficulties are not surprising, as structure–odor relationships are several orders of magnitude more complex than their pharmacological counterparts, structure–activity relationships.[21] More recently, the simplifying “steric theory” of Amoore has evolved into the olfactophore concept. Olfactophores, like pharmacophores, describe the spatial molecular arrangement of interacting groups and were found to be helpful for the computer-aided design of new odorants.[22] Such models were constructed without prior knowledge about the receptor site.

In 1991, Axel and Buck published a study that contributed considerably to our understanding of the molecular basis for the olfactory perception process.[4] To assess the presence of potential receptors in the olfactory epithelium they postulated that OR proteins belong to the family of G-protein-coupled receptors (GPCR). GPCR proteins are embedded in the surface membrane of cells and cross this membrane seven times. They are made up of seven helices, which are joined together by three extracellular and three intracellular loops. These transduction proteins can receive chemical signals outside the cell and transmit them into the interior of the cell. The receptor activates the intracellular G protein, which causes effectors to produce a second signal inside the cell. This second signal causes the cell to react to the original external chemical signal. A simplified schematic representation of the transmembrane protagonists is presented in Figure 1.

Prior to their interaction with transmembrane OR proteins, odorants are thought to be associated with odorant-transport (OT) proteins present in mucus.[23,24] OT proteins belong to a class of carrier proteins present in physiological...
fluids. They contribute actively to the transportation of the odorant from the inhaled airstream through the mucosa to the cilia of the olfactory neurons.

The basic approach of Axel and Buck was to design probes that could recognize DNA sequences that encode proteins located in the olfactory epithelium. A new class of genes were found that express a previously unknown family of GPCR-type proteins, the so-called OR proteins. The derived molecular structure of an OR protein is depicted in Figure 2 together with a complex of the odorant 2-isobutyl-3-methoxypyrazine with an OT protein.

Gene analysis revealed that the OR proteins had highly variable sequences and that they were only encoded in the olfactory epithelium. From then on, a tremendous number of studies were performed to determine the number and functions of OR proteins. By searching the human genome database, Buck and co-workers identified 339 intact OR genes and 297 OR pseudogenes. Sequence comparison led to the classification of the human OR proteins into 172 families. It was shown that a single OR protein can be activated by multiple odorants and that a single odorant can activate several OR proteins. As a consequence, different odorants are recognized by different combinations of receptors, some of which are closely related to one another. Numerous odorants activate distinct sets of OR proteins, even if overlaps between these sets can exist. From these results, the molecular basis for the first steps of olfaction was identified, namely, that olfactory perception proceeds through a combinatorial process. Indeed, given the large number of OR proteins, this combinatorial process could permit discrimination between a vast range of chemicals. Buck and co-workers estimated that even if an odorant activated only three receptors (in fact many more are activated), the number of theoretically discriminable odorants should be close to a billion. The biological method of chemical recognition is therefore far removed from the simple “lock and key” analogy. These findings are fully consistent with the potential discrimination of a very large number of chemical compounds with different structures and shapes, as well as distinct odors.

The sequence of the OR proteins was determined indirectly through examination of the DNA sequence. Generally, three-dimensional protein structures can be determined through direct measurements by X-ray crystallography, electron microscopy, and NMR spectroscopy. These techniques are, however, suitable only for water-soluble proteins, and not for GPCR proteins, which require precisely balanced physicochemical conditions for structural and functional integrity. As such conditions are difficult to achieve, new techniques, such as two-dimensional cryomicroscopy, have to be employed to attempt the elucidation of these structures. Therefore, the amount of
experimental information available on the three-dimensional structure of GPCR proteins is limited. So far, only the rhodopsin GPCR structure has been determined by direct measurements.[33] The structures of OR proteins have been derived from rhodopsin-based models.[34] Recent studies started to evaluate the differential responses of a receptor to a broad variety of agonists.[35] Much progress has been made towards understanding the molecular basis of olfactory perception, but many questions remain unanswered because of its combinatorial nature.

The pioneering transdisciplinary studies of Axel and Buck have tremendous implications for flavor and fragrance research. Knowledge about the molecular interactions between OR proteins and odorants can contribute to the evaluation of the interaction of a specific odorant with a given set of OR proteins, a strategy that has already been patented.[36] The combinatorial aspect of information processing in the olfactory bulb and the perception of odor by pattern recognition throw light on the success and failure of previous approaches based on studies of structure–odor relationships and olfactophore modeling. After the confirmation of the three-dimensional OR protein structure, chemists will be in a better position to undertake the rational design of odorants for the activation of specific OR proteins. However, for practical applications, odorants are seldom used as pure compounds, but rather as mixtures, which may be very complex. Thus, the successful application of odorants will always depend on their formulation. The field for the search for new odorants, deodorants, and odor modifiers is wide open.

[3] “If you can answer that question, the Nobel Prize is yours.” Nice-Matin, 2 April 1970.
[21] Until now, the odorant-transport protein was denoted odorant-binding (OB) protein. Herewith, we suggest the label OT protein, because 1. the term “binding” is not specific enough to describe the hydrophobic chemical interaction between odorant and protein, and 2. the term “transport” can describe the processes of inclusion, delivery, and release of the odorant molecule to the OR protein.
[23] The structure of the OT protein was taken directly from X-ray crystallographic data (PDB id. 1DZK). The three-dimensional structure of the OR protein was derived by analogy with the experimentally determined structure of rhodopsin; see reference [33].