Bioinspired nose devices and their potential application for non-invasive olfactory detection of pathologies

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Our work on bioinspired nose devices was carried out in the framework of 2 successive European projects: SPOT-NOSED (Single PrOTein NanObioSEnsor griD array) 2003-2006 and BOND (Bioelectronic Olfactory Neuron Device, http://bondproject.org/) 2009-2012, aimed at using ORs carried by nanoscale liposomes as sensing elements of an electrochemical array, for specifically detecting target odorants from complex odorant mixtures. These projects have potential applications in medical diagnosis, but also in agroalimentary or cosmetics quality control, security, and environment.

In the natural mammalian olfactory system, more than a thousand ORs exhibit various levels of specificity and sensitivity to odorants. For bioinspired nose devices dedicated to detecting a target VOC, the relevant ORs to monitor this target odorant first have to be identified by single-cell RT-PCR on neurons exhibiting a calcic response to this odorant. In addition, we developed a dedicated procedure that (i) automates homology modeling of mammalian ORs based on the available 3D structures of G protein-coupled receptors and (ii) performs the docking of odorants on these models and scores the complexes. Since ORs exhibit low sequence similarities with other GPCRs, a fold recognition technique is used to obtain a robust initial alignment. An analysis of the resulting in silico complexes for a previously characterized human OR suggests interesting results as to the docking position of antagonists or agonists relative to the putative binding pocket (http://genome.jouy.inra.fr/GPCRautomodel) [1]. Visualizing the complexes allows the identification of key functional residues involved in the process of ligand recognition, which can help refining the choice of the ORs best suited to bind a given odorant.

The selected ORs are then tagged and heterologously expressed in S. cerevisiae. ORs functionality can be tested in yeast membrane fraction by Bioluminescence Resonance Energy Transfer [2]. Sonication of the membrane fraction yields natural nanoscale vesicles carrying the ORs on their lipid bilayer. The deposition of these nanovesicles onto substrates is monitored by Atomic Force Microscopy: nanovesicles flatten without rupturing on glass substrates, with reproducibly high substrate coverages. Surface chemistry modification of gold substrates indicates a higher affinity of natural nanovesicles for acid modified surfaces. Nanosomes grafting is performed most efficiently onto surfaces functionalized by activated carboxylic thiol SAMs [3].

The active part of the bioelectronic sensor consists of a silicon nanoelectrode with an electrochemical cell and a dedicated electronic chip. To provide the sensor with high sensitivity, gold nanoparticles can be generated on the gold surface by electrochemical chronoamperometry to favor nucleation. Gold nanoparticles induce a surface area increase, thus immobilization of a larger amount of nanosomes, measured by Atomic Force Microscopy and by a decrease in charge transfer resistance in Electrochemical Impedance Spectroscopy. The tagged receptors can be specifically immobilized on surfaces carrying antibodies against the tag, as monitored by electrochemical measurements.

Nanoelectrodes are fabricated using e-beam lithography, with sizes in adequate with the nanosomes. Adequate nanoelectronics for low-noise and wide-bandwidth measurements is designed to be directly connected to the nanoelectrodes. Significant changes in Electrochemical Impedancemetric Spectroscopy measurements are monitored along the process of electrodes functionalization, nanosomes grafting, and finally upon ORs conformational change induced by odorant binding.

Using this whole concept, prototypes exhibiting very low detection thresholds comparable to the animal nose were conceived [4].

References