# [P4] Agonists of G protein coupled-odorant receptors are predicted from chemical features

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G protein-coupled receptors (GPCRs), the targets of nearly 30% of all modern therapeutic drugs, are seven transmembrane proteins converting extracellular stimuli into intracellular signals in a wide variety of cell types.[1] In the human nose, odor detection by olfactory sensory neurons (OSNs) depends on a large family of G protein-coupled odorant receptors (ORs) which represent 4% of our proteome.[2] Recent studies also report the presence of such receptors in many non-olfactory tissues.[3] Understanding the characteristics of the compounds these receptors get activated by becomes increasingly relevant.[4]

Here, the activity of 258 chemicals on the human G protein-coupled odorant receptor (OR)51E1, also known as prostate-specific G protein-coupled receptor 2 (PSGR2) [5] was virtually screened by machine learning using 4884 chemical descriptors as input. A systematic control by functional *in vitro* assays revealed that a support vector machine algorithm accurately predicted the activity of a screened library. It allowed identifying two novel agonists *in vitro* for OR51E1. The transferability of the protocol was assessed on OR1A1, OR2W1, and MOR256-3 odorant receptors and in each case, novel agonists were identified with a hit rate ranging from 39% to 50%. We further show how ligands' efficacy is encoded into residues within OR51E1 cavity using a molecular modelling protocol. Our approach allows widening the chemical spaces associated with odorant receptors.[6] This machine learning protocol based on chemical features thus represents an efficient tool for screening ligands for G protein-coupled odorant receptors that modulate non-olfactory functions, or upon combinatorial activation, give rise to our sense of smell.

Bibliography:

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