

Making sense of scents: structural insights into odor detection
Vanessa Ruta, Rockefeller University/HHMI

Olfactory systems must detect and discriminate an enormous diversity of chemicals in the environment. To contend with this challenge, diverse species from humans to insects, have converged on a common strategy in which odor identity is encoded through the combinatorial activation of large families of olfactory receptors, thus allowing a finite number of receptors to detect an almost infinite chemical world. Central to this sensory coding strategy is that most individual receptors can be activated by a variety of structurally and chemically diverse odorants, suggesting that odorant detection does not adhere to the classic lock and key mechanism that governs many receptor-ligand interactions. Yet how such flexible chemical recognition is achieved has remained elusive. Our lab has been using the insect olfactory system as a window into the structural logic of odor detection. In recent work, we used cryo-electron microscopy to elucidate the structure of a broadly-tuned insect olfactory receptor, MhOR5, in multiple gating states—alone, and bound to two of its ligands. These structures, along with molecular docking and functional analysis of receptor tuning, suggest that odorant recognition relies predominantly on non-directional hydrophobic interactions formed with residues distributed across multiple surfaces of the binding pocket, offering a structural basis for this receptor's promiscuous chemical tuning. Our work thus begins to shed light onto the molecular recognition mechanisms that ultimately endow the olfactory system with its immense discriminatory capacity.