The nose has it

Understanding how a few hundred receptors in the nose can decode millions of different odours is leading to better protection for the body all round | **S.L Mintz**

THAT the nose knows is hardly news. But for discovering just how the nose knows, Richard Axel and Linda Buck, molecular biologists respectively at Columbia University in New York and the Fred Hutchinson Cancer Research Centre in Seattle, shared the 2004 Nobel prize in physiology or medicine. Until they found one-to-one links between genes and odour receptors, and mapped the code that lets a few hundred receptors discern a vast array of chemical odours, the sense of smell eluded explanation.

Of the five senses, smell performs a particularly rigorous job. Sight and sound operate along well-defined spectra; touch perceives an object's texture and temperature; and taste, except chiefly for sourness or sweetness, turns out to be mostly a matter of smell.

The nose, however, must distinguish random differences among innumerable airborne odours and transmit them faithfully to the brain. No continuum organises the chemicals that produce odours, and differences can be subtle. Tweak a molecule that smells like pear, for instance, and it becomes banana.

When a chemical molecule enters the nose, it finds its way to specialised receptors embedded in the mucous membrane. Rats, the first creatures to surrender their olfactory blueprint, rely on more than 1,200 receptors. In humans, 350 active receptors, each the product of a single gene, stand guard. Another 600 olfactory "pseudo-genes" no longer sponsor receptors, an evolutionary consequence of less reliance on smell. All told, olfactory genes comprise about 3% of the human genome, a much larger population than other senses require. Sight makes do with three genes and taste with 29—evidence of smell's complex challenge.

To understand how receptors distinguish lilac or apple pie from soured milk or cleaning solvent, imagine receptors as an alphabet with 350 letters. Every chemical triggers multiple receptors; resulting combinations spell distinct odours. Do the arithmetic, says Dr Buck, and you'll find ample capacity to detect far more than 100,000 chemical odours adrift in the environment. Odour receptors trip neural impulses that no- ▸▸

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tify the olfactory bulb which, in turn, notifies regions of the brain where smell taps primal dimensions. As the novelist Italo Calvino observed, "Food, non-food; our cave, the enemy's cave; danger—everything is first perceived by the nose, everything is within the nose, the world is the nose."

Cracking the molecular code that governs smell has not yet revealed which receptor responds to vintage red wine, exotic perfume or Godiva chocolate. So far, scientists have identified only a handful of such links. So, touchy-feely aromatherapy still awaits a thorough molecular rundown.

But much more is at stake. Olfactory sensory neurons put "G-protein coupled receptors" (GPCRS) to work, and so do all other cells in the body. "The same family of molecules is responsible for chemical communication in the brain and other organ systems," says Columbia's Dr Axel. If you want someone to move, you have to wave or shout. To make receptor cells in the nose or elsewhere behave, you have to adjust their scent for neurotransmitters such as serotonin or dopamine.

With this in mind, Compellis Pharmaceuticals, a small drugmaker in Boston, Massachusetts, hopes to woo dieters with a nose spray that blocks the aromas that make food irresistible. The spray still faces clinical trials, however, before it can land on drug-store shelves.

As nature's preferred way to detect environmental chemicals, GPCRS may yield a key to accelerating drug development. A small fraction of known GPCRS now furnish drugs that fetch more than $30 billion in annual sales. In New York, Sentigen Biosciences is zeroing in on uncharted "orphan receptors" that appear to promise rich therapeutic and financial returns for the fledgling company. Dr Axel, who is Sentigen's chief scientific consultant, calls "de-orphanisation" the most exciting commercial application of olfactory research.

Predicting chemical interaction is crucial to the success of new and improved drugs. According to Sentigen's boss, Joseph Pagano, the company has devised a method with potential for testing simultaneously the cross-reactivity of all drugs that target known GPCRS—a much more efficient process than testing them one at a time.

If they pass these tests, drugs derived from de-orphanised GPCRS would offer the most promise for patients with conditions that respond poorly or unpredictably to existing drugs, such as strokes, neuro-inflammation and anxiety.

With a licence to harness findings from Dr Axel's laboratory at Columbia University, Sentigen is pursuing applications in pest control and homeland security. In particular, the war on terrorism has enlisted Sentigen to figure out how dogs find explosives—and perhaps one day endow a computer chip with the same ability.

Picture a synthetic police dog that always operates at peak efficiency, says Sentigen's vice-president of research, Kevin Lee. Even with $1.6m over two years from a number of government agencies, creating a chip with the sensitivity, versatility and chemical range of a canine nose poses a formidable challenge.

Odour receptors do not yet work outside of a living cell. But that will change if Dr Axel's philosophy prevails. "As scientists", he says, recalling the poet William Blake, "we are defining areas that have not been understood before. That which is proven was once only imagined." If so, then nosing around might just pay off.

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